Universidade de Aveiro
2015

Secção Autónoma das Ciências da Saúde

Adriana Filipa da Silva Ferreira

Curricular Training Report: Clinical Trials Coordination in Neurology

Relatório de Estágio Curricular: Coordenação de Ensaios Clínicos em Neurologia

Universidade de Aveiro
2015

Secção Autónoma das Ciências da Saúde

Adriana Filipa da Silva Ferreira

Curricular Training Report: Clinical Trials Coordination in Neurology

Relatório de Estágio Curricular: Coordenação de Ensaios Clínicos em Neurologia

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado Convidado da Faculdade de Medicina da Universidade de Lisboa, e da Professora Doutora Maria Joana da Costa Gomes da Silva, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro.

o júri

Presidente	Professor Doutor Bruno Miguel Alves Fernandes do Gago Professor Auxiliar Convidado, Universidade de Aveiro
vogal – arguente principal	Professor Doutor José Carlos Fontes das Neves Lopes Professor Auxiliar, Universidade de Aveiro
vogal – orientador	Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta, Universidade de Aveiro

agradecimentos

Gostava de agradecer a todos os que tornaram este estágio possível. Em primeiro lugar, aos meus orientadores, Professor Joaquim Ferreira e Professora Joana Silva, pelo conhecimento que me transmitiram, compreensão e apoio ao longo desta etapa. Muito obrigada pelas oportunidades de aprendizagem e pela orientação ao longo do estágio.

O meu sincero obrigado aos diretores do Mestrado em Biomedicina Farmacêutica, Professor Luís Almeida e Professor Bruno Gago, pela formação e pelas oportunidades nos últimos dois anos.

À Dra. Ana Noronha, pelo carinho com que me recebeu, pela partilha de conhecimento e pela confiança que depositou em mim. Um obrigado especial por acreditar nas minhas capacidades e por fazer de mim sempre uma melhor profissional.

À Dra. Ana Teresa, Dra. Daisy de Abreu, Dra. Nilza Karina, Dra. Raquel Lobo, Dra. Ana Marta Anes, Dra. Nádia Espada e Carolina Gaspar por toda a disponibilidade para ajudar.

Um obrigado especial à Ana Salgueiro e à Andreia Rocha pela companhia durante este período, pela ajuda e pela amizade. À Carla Rodrigues e à Ana Augusto pelas experiências e ao Márcio Barra pelas oportunidades e pelo apoio.

À Inês Carreira, Berta Lima, Diana Silva, Ângela Figueiredo e Carolina Amorim, um obrigado muito sincero pela amizade, pela motivação constante e apoio incondicional. Mesmo longe vocês estão perto.

À minha prima Patrícia Lopes, por acreditar sempre em mim, por fazer de mim a pessoa que sou hoje e por me ajudar a alcançar o que alcancei. Foste e sempre serás a minha maior fonte de motivação.

Ao Daniel Cruz, muito obrigada por estares ao meu lado e por me incentivares a ser sempre melhor. Obrigada pela paciência e pelo carinho.

Tudo tenho a agradecer aos meus pais Maria Assunção e Serafim Ferreira. Obrigado pelo amor, encorajamento e apoio incondicionais, pela educação e pelos sacrifícios que fizeram para que eu pudesse chegar até aqui. Não podia ter mais orgulho em vocês e estar mais agradecida.

palavras-chave

Investigação Clínica, Ensaios Clínicos, Estudos Observacionais, Coordenação de Ensaios Clínicos, Gestão de Dados Clínicos, Escrita Científica, Farmacovigilância, Neurologia, Biomedicina Farmacêutica

resumo

O presente relatório descreve as atividades desenvolvidas durante o estágio curricular como coordenadora de investigação clínica, que teve lugar na Unidade de Farmacologia Clínica do Instituto de Medicina Molecular e decorreu de Setembro de 2014 a Junho de 2015.

A principal atividade desempenhada durante este estágio foi a coordenação de ensaios clínicos na área da neurologia, nomeadamente ensaios de fase II, III e IV. Foram desenvolvidas outras atividades, tais como gestão de dados clínicos, atividades de farmacovigilância e escrita científica e monitorização de estudos clínicos, com vista a complementar a formação curricular.

Neste relatório é, também, apresentada uma breve contextualização do estado de arte do processo de Investigação & Desenvolvimento de novos medicamentos, tendências atuais e especificidades do desenvolvimento de medicamentos na área da neurologia. Para além disso são abordadas as dificuldades sentidas durante o estágio e as estratégias utilizadas para as ultrapassar, bem como a visão pessoal sobre o papel do coordenador de investigação clínica na condução de ensaios clínicos.

Globalmente, a realização deste estágio curricular traduziu-se na oportunidade de aplicar e aprofundar os conhecimentos e competências adquiridos ao longo do percurso académico, em especial no Mestrado em Biomedicina Farmacêutica, e de desenvolver competências e aptidões, tanto a nível profissional como pessoal, fulcrais para um profissional de investigação clínica. Em conclusão, este estágio constituiu uma introdução à prática da investigação clínica.

keywords

Clinical Research, Clinical Trials, Observational Studies, Clinical Trials Coordination, Clinical Data Management, Medical Writing, Pharmacovigilance, Neurology, Pharmaceutical Biomedicine

abstract

This report describes the activities developed during the curricular training as coordinator of clinical research, which took place in the *Unidade de Farmacologia Clínica* of the *Instituto de Medicina Molecular* and was held from September 2014 to June 2015.

The main activity performed during this training was the coordination of clinical trials in the field of neurology, mainly phase II, III and IV clinical trials. Other activities, such as data management, pharmacovigilance, medical writing and monitoring of clinical studies, were developed to complement the training.

This report also presents a brief background of the state of the art of the Research & Development process of new drugs, current trends and specificities of the drug development in neurology. Furthermore, it addresses the difficulties experienced during the training and the strategies used to overcome them, as well as a personal insight on the role of the clinical research coordinator in conducting clinical trials.

Overall, achieving this curricular training resulted in the opportunity to apply and deepen the knowledge and skills acquired throughout the academic career, especially in the Masters in Pharmaceutical Biomedicine, and to develop skills and abilities, at professional and personal level, central to a professional of clinical research. In conclusion, this training was an introduction to the practice of clinical research.

Table of Contents

1. Introduction 1

1.1. Vision of the Host Institution 1

1.1.1. Sub-Unidade de Bioestatística e Metodologia 3

1.1.2. Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo 4

1.1.3. Centro de Investigação Clínica 5

1.2. Objectives 8

1.3. State of the Art of the Pharmaceutical R&D Process and the R&D in Neurology .. 8

1.3.1. The Pharmaceutical R&D Process: Overview, Challenges and Trends 9

1.3.2. The R&D Process in Neurological Diseases 10

1.3.3. Trends and Directions in CNS Drug Development 12

1.3.4. Clinical Trials 13

2. On-the-Job Training 22

2.1. Generic Training 22

2.1.1. Training on the Ongoing Studies and Organization of the CIC 23

2.1.2. Data Management Activities 24

2.1.3. Pharmacovigilance Activities 25

2.1.4. Medical Writing Activities 29

2.1.5. Other Activities 31

2.2. Specific Training 33

2.2.1. Initial Training Activities 34

2.2.2. Setting Up a Clinical Trial 37

2.2.3. Running a Clinical Trial 39

3. Discussion 49

4. Conclusion 55

5. References 57

List of Figures

Figure 1. Structure and organization of the UFC. 2

Figure 2. Number of clinical trials and observational studies conducted at CIC, from 1999 to the first semester of 2015, by neurologic disorder 6

Figure 3. The current pharmaceutical R&D process. 9

Figure 4. Comparison between R&D metrics in neurological disorders and non-neurological disorders. 11

Figure 5. Number of clinical trials submitted to and approved by INFARMED and sponsored by the pharmaceutical industry and by academic institutions, from 2006 to 2014, in Portugal. 17

Figure 6. Number of clinical trials submitted to INFARMED from 2006 to 2014, by therapeutic area. 20

Figure 7. Timeline of the main activities developed in the generic training. 23

List of Tables

Table 1. Clinical trials ongoing in CIC in which I actively collaborated. 33

Table 2. Study coordination activities performed in the different clinical trials. 34

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CIC	Centro de Investigação Clínica (Clinical Research Center)
CNS	Central Nervous System
CRC	Clinical Research Coordinator
CRF	Case Report Form
EC	European Commission
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EU	European Union
EMA	European Medicines Agency
GCP	Good Clinical Practice
HSM	Hospital de Santa Maria (Hospital of Santa Maria)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMI	Innovative Medicines Initiative
IMM	Instituto de Medicina Molecular (Institute of Molecular Medicine)
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde (National Authority of Medicines and Health Products)
IRT	Interactive Response Technology
ISF	Investigator Site File
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response Systems
MedDRA	Medical Dictionary for Regulatory Activities
NOACs	Non-vitamin K Oral Antagonist Anticoagulants
PI	Principal Investigator
R&D	Research and Development
Portal RAM	Portal de Reações Adversas a Medicamentos (Portal of Adverse Drug Reactions)
SAE	Serious Adverse Event
SNF	Sistema Nacional de Farmacovigilância (National Pharmacovigilance System)
SVIG	Sistema de VIGilância (Vigilance System)

UFC	Unidade de Farmacologia Clínica (Clinical Pharmacology Unit)
URFLVT	Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo (Regional Pharmacovigilance Unit of Lisbon and Tagus Valley)

1. Introduction

This curricular training report presents an overview of the activities performed as trainee in clinical trials coordination, from September 2014 to June 2015. This training was carried out within the scope of the Master's degree in Pharmaceutical Biomedicine and took place at *Unidade de Farmacologia Clínica* (UFC, Clinical Pharmacology Unit), one of the research units of the *Instituto de Medicina Molecular* (IMM, Institute of Molecular Medicine), an associate laboratory of the Portuguese Ministry for Education and Science.

During the training I had the opportunity to actively participate in several activities relating to different stages of the development of new health interventions, mainly new drugs, and to support others. These activities include not only coordination of clinical trials but also management of clinical data, writing of scientific papers and performance of pharmacovigilance activities, from the perspective of the regulatory authority.

This report provides a characterization of the UFC, defining where it fits in the clinical research framework, its purposes, organization and work developed, followed by the identification of the objectives defined for this curricular training, and by an overview of the Research and Development (R&D) process of new drugs, highlighting the particularities of the R&D process in neurological diseases. The activities performed during this ten-month period are then described, with more emphasis for the activities of clinical trials coordination, as well as a brief theoretical overview on topics that contextualize the activities described.

A discussion about the training experience and a summary of the importance of each of the activities performed to the successful planning, conducting, management and reporting of clinical projects, mainly clinical trials, are presented.

1.1. Vision of the Host Institution

The UFC is a research unit of IMM, a private, non-profit association mainly supported by national public funds and European Union (EU) funds that aims to foster basic, clinical and translational biomedical research to better understand diseases, contribute to the development of diagnostic and prevention tools and to develop new and efficient therapeutics (1). The unit was formally created on the 1st of July 2013 based on the research team from the *Unidade de Neurofarmacologia* (Neuropharmacology Unit) of the *Unidade Neurológica de Investigação Clínica*

(Neurological Clinical Research Unit) of IMM and the members of the *Laboratório de Farmacologia Clínica* (Laboratory of Clinical Pharmacology) of *Faculdade de Medicina da Universidade de Lisboa* (Medicine Faculty of University of Lisbon) (2).

As a research unit of IMM, the UFC shares with it its overall objectives. The UFC aims to contribute to the development of effective and safe therapeutic interventions through the establishment of optimized methodologies for the design, conduction, analysis and report of clinical trials (3). The research activity of UFC is focused on neurodegenerative diseases, particularly Parkinson's disease and Huntington's disease, specific populations, mainly late stage disease populations, and orphan interventions, such as rehabilitation and non-pharmacological interventions (3).

The main clinical pharmacology domains of interest of the UFC are clinical trials methodology, with particular interest on novel, early phase proof-of-concept clinical studies and innovative trial designs and methodologies, outcomes, systematic reviews, drug safety and utilization and pharmaco-magnetic resonance imaging (4). The UFC establishes collaborations with the pharmaceutical industry to facilitate the conduction of clinical trials by supporting in early stages of drug development and planning of clinical development (4). Furthermore, the UFC is also committed to organize and provide comprehensive clinical pharmacology services to other research groups of the *Centro Hospitalar Lisboa Norte* (Hospital Center of North Lisbon), *Faculdade de Medicina da Universidade de Lisboa* and IMM, to educate and train in clinical trials methodology and Good Clinical Practice (GCP) and to foster investigator-initiated trials (3).

The research activity of the UFC is funded through participation in several national and international projects. During the period of 2014/2015, the UFC was involved in eight projects, most of them related to Parkinson's disease. Currently, the UFC integrates six different sub-units, as shown in Figure 1, that relate to each other and cooperate to achieve the overall objectives of the unit (3).

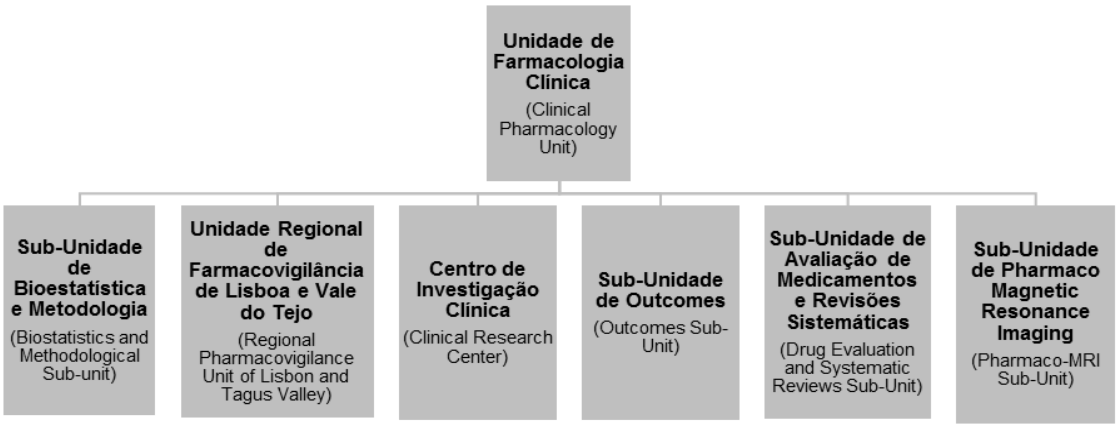

Figure 1. Structure and organization of the UFC. Adapted from (3).

The *Sub-Unidade de Outcomes* (Outcomes Sub-Unit) is facilitated by Professor Joaquim Ferreira and co-facilitated by Dr. Ricardo Fernandes, a clinical researcher affiliated with the UFC, and is focused on the study of measurement instruments, including biomarkers and patient-reported outcomes, in drug evaluation (2). The *Sub-Unidade de Avaliação de Medicamentos e Revisões Sistemáticas* (Drug Evaluation and Systematic Reviews Sub-Unit) is facilitated by Professor João Costa, Coordinator of the *Centro Português Cochrane* (Cochrane Portuguese Center) and Vice-Director of the *Centro de Medicina Baseada na Evidência* (Center of Evidence-Based Medicine) of the *Faculdade de Medicina da Universidade de Lisboa*. This research sub-unit corresponds to the *Grupo Cochrane de Doenças do Movimento* (Cochrane Movement Disorders Group) and its principal function is to create and maintain a register of trials in movement disorders to provide reviewers, facilitating the development of systematic reviews (2). The *Sub-Unidade de Pharmaco-Magnetic Resonance Imaging* (Pharmaco MRI Sub-Unit) is facilitated by Dra. Sofia Reimão, a clinical researcher affiliated with the UFC, and, through application of neuroimaging techniques, works to detect micro-structural, functional and biochemical alterations in Central Nervous System (CNS) related to neurological diseases (4).

The remaining research sub-units of UFC correspond to the sub-units where my curricular training took place. What follows is a detailed description, in chronological order according to the course of the training, of their objectives, constitution and main activities developed.

1.1.1. Sub-Unidade de Bioestatística e Metodologia

The *Sub-Unidade de Bioestatística e Metodologia* is a research sub-unit of the UFC that is focused on management of investigator driven research projects, statistical analysis of clinical data, medical writing, project management, and other support activities (4).

This sub-unit provides statistical support to all research projects of the UFC, mainly those related with design and analysis of clinical trials and systematic reviews, as well as methodological support on design, conduction, analysis and reporting of clinical research studies, and optimization of study design and feasibility (2). The sub-unit also provides logistical support to the vast majority of the projects of the UCF (2).

The research group is facilitated by Professor Joaquim Ferreira and integrates two biostatistics, one data manager and two project managers. The group develops a wide range of activities that include mainly the development of databases, clinical data management and statistical analysis of clinical data, performance of quality control and de-identification activities, writing and submission of scientific papers, development of

research protocols and other research related documentation, and development and submission of scientific projects. Despite the responsibilities and functions of each person are well defined, there is a strong collaboration between all members of the group for the performance of the different activities.

The *Sub-Unidade de Bioestatística e Metodologia* is engaged in several research projects, most of them in collaboration with other national and international research institutes (3).

1.1.2. Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo

The *Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo* (URFLVT, Regional Pharmacovigilance Unit of Lisbon and Tagus Valley) is one of the four sub-units of the *Sistema Nacional de Farmacovigilância* (SNF, National Pharmacovigilance System) (2).

The SNF is an organized system that is focused in the monitoring of the safety of authorized medicinal products and in the detection of any change to their risk-benefit profile, in order to support decision making at various levels of the healthcare system (5). The URFLVT, as a structure of the SNF, shares with it its overall objectives, which are making more efficient the collection, treatment and study of pharmacovigilance data to enable the timely intervention, by responsible authorities, to ensure the quality, effectiveness and safety of medicines placed on the market (6).

The URFLVT comprises the steering committee, Dr. Mário Miguel Rosa, senior expert at European Medicines Agency (EMA) and consultant at *Autoridade Nacional do Medicamento e Produtos de Saúde* (INFARMED, National Authority of Medicines and Health Products), who is responsible for defining the program of activities of the URFLVT and for coordinating those activities, the scientific board, consisting of individuals with recognized expertise in health sciences and whose function is to advise the steering committee on priorities, procedures and others, and the human resources (6). The human resources of URFLVT include one physician and two pharmaceuticals with training and experience in pharmacovigilance and one administrative to provide secretarial support with a high degree of autonomy (6). One of the pharmaceuticals also assumes the role of quality manager (6).

The area of influence of URFLVT covers all healthcare units of Lisbon and Tagus Valley, comprising public and private healthcare units, which corresponds to a population of 3,659,868 inhabitants (according to a public survey from 2011) (6). The activities developed in this sub-unit of the UFC include reception, validation, classification and processing of spontaneous reports of suspected Adverse Drug Reactions (ADRs), including causality assessment, dissemination and promotion of the

reporting of suspected ADRs in the geographical area of Lisbon and Tagus Valley, bringing forward proposals for the realization of pharmacoepidemiology studies within the scope of the SNF, conducting training activities in the context of pharmacovigilance, preparation of relevant information to distribute to other regional units or international authorities and detection of safety signals in the context of pharmacovigilance (6).

All the activities of URFLVT are performed in close collaboration with INFARMED, which is the entity responsible for ensuring the proper functioning of the SNF (5,6).

1.1.3. Centro de Investigação Clínica

The *Centro de Investigação Clínica* (CIC, Clinical Research Center) is the sub-unit of the UFC that is dedicated to setting up and running clinical studies – clinical trials and observational studies (2). It provides a logistics structure that facilitates the conduction of clinical studies, ensuring the requirements for the recruitment, evaluation, registration of information and follow-up of research participants (2). The CIC has competence to perform almost all activities required by study protocols, except for complementary exams. The vast majority of the clinical studies conducted at CIC are industry sponsored. However, the CIC also supports the establishment of investigator driven studies.

The CIC is dedicated to the conduction of clinical studies in neurology, mainly movement disorders and dementia, according to all applicable procedures, legislation and regulations, namely GCP, and aligning the research activity with clinical care delivery (2). The number of clinical studies carried out at CIC between 1999 (year in which the group started activities) and the first semester of 2015, according to an internal database, are presented in Figure 2, by neurologic disorder and distinguishing clinical trials from observational studies. Parkinson's disease is the neurologic condition with the highest number of clinical trials conducted, with 38 trials, followed by Alzheimer's disease (17 clinical trials), Multiple Sclerosis (15 clinical trials) and Epilepsy (13 clinical trials). Regarding observational studies, CIC has conducted, essentially, studies in Multiple Sclerosis.

According to the same internal database and considering the distribution of the clinical trials conducted at CIC by study phase, phase III clinical trials correspond to the majority of clinical trials conducted, with 70 clinical trials conducted since the group has started functions, followed by phase II with 18 clinical trials, phase II/III with eight,

phase IIb with six, phase IIIb with five, phase IV with three and phase I with only one clinical trial.

During my training at CIC, there were 22 clinical trials ongoing, most of all in Alzheimer's disease (6), Epilepsy (4), Familial Amyloid Polyneuropathy (4), Multiple Sclerosis (3) and Parkinson's disease (3), and 10 observational studies, mainly in Multiple Sclerosis (5) and Huntington's disease (2).

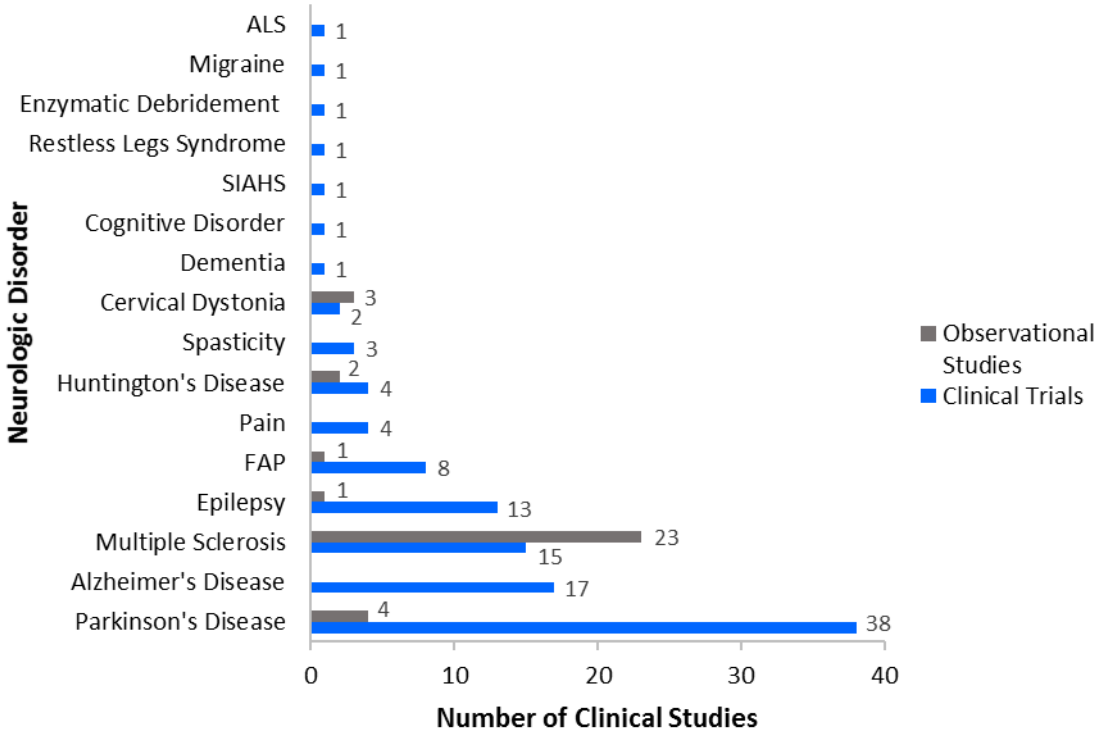

Figure 2. Number of clinical trials and observational studies conducted at CIC, from 1999 to the first semester of 2015, by neurologic disorder. Adapted from an internal database. (Amyotrophic Lateral Sclerosis: ALS; Familial Amyloid Polyneuropathy: FAP; Syndrome of Inappropriate Antidiuretic Hormone Secretion: SIAHS)

The research group of CIC includes people with different backgrounds and expertise that work together to ensure the safety of the research participants and that the study protocol and the applicable regulations are consistently followed. Overall, the research group includes 19 investigators, mostly physicians from *Hospital de Santa Maria* (HSM) and researchers from IMM, seven study nurses, five psychologists, four pharmacists, two Clinical Research Coordinators (CRCs) and one laboratory technician. The roles and responsibilities of each member of the group are delegated according to their qualifications and are briefly described below:

- **Principal Investigators (PIs)** have the primary responsibility for ensuring the ethical conduct of the clinical trials, which includes providing adequate medical care to clinical trial participants and protecting their safety and well-being during the trials, and for ensuring protocol compliance and adherence to institutional, national and international regulations and guidance. The PIs also oversee all aspects of a clinical trial from recruitment to data collection and analysis and interpretation of results.
- **Sub-Investigators/ Co-Investigators** may perform all or some of the PIs functions, which include performing study-related procedures and/or making important study-related decisions in compliance with the ethical and legal requirements and under the supervision of the PIs.
- **Clinical Research Coordinators** coordinate the daily activities of the clinical trials, working closely with the research team to ensure that all protocol required procedures and visits occur according to protocol specified guidelines. The CRCs are also responsible for data management of the trials, which includes accurate and timely data entry in electronic databases and resolution of any data queries that may be generated. At CIC, it is also responsibility of CRCs to collaborate in the submission and approval process of the trials, help in the establishment of financial agreements and perform the overall fiscal management of the trials.
- **Research Nurses and Laboratory Technician** are responsible for collecting biological samples from participants, as well as giving overall support to the rest of the research team. The study nurses are also responsible for performing some invasive procedures according to the research protocols.
- **Research Psychologists** are responsible for evaluating, diagnosing and studying behavior and mental processes of participants through the application of specific clinical scales defined by the research protocols.
- **Research Pharmacists** ensure procedures are followed for the control of medications used in clinical trials. They order, store, and dispense research medications, provide information to the patient about trial medications and oversee patient compliance.

The CIC works in strong collaboration with the HSM in the recruitment of volunteers to participate in clinical studies. Besides this collaboration, over the last years, the CIC has also established collaborations with several other national and international research centres and has been involved in clinical research networks with a scope extending throughout the translational continuum (2).

1.2. Objectives

For this curricular training I defined a set of objectives that I considered key to achieve a proper training in clinical trials coordination – primary objectives. The multidisciplinary characteristics of the UFC allowed me to develop several other activities related to the development of new health interventions. Therefore, I defined other objectives – secondary objectives – that represented specific aspects I would like to develop and acknowledge, in the context of clinical research.

Primary objectives:

- To acquire skills and qualification in coordination of clinical trials and observational studies;
- To perform the daily activities of a CRC;
- To apply and complement the previously acquired academic knowledge in a clinical research context;
- To develop and improve my personal and soft skills, such as communication, self-confidence, critical thinking, problem solving, organization, autonomy and responsibility.

Secondary objectives:

- To acquire empirical knowledge on clinical trial monitoring;
- To understand the structure, role and workflow of a regional pharmacovigilance unit;
- To acquire skills in the reception, validation and processing of spontaneous reports of ADRs;
- To acquire knowledge and basic skills in clinical data management and quality control procedures;
- To practice medical writing skills;
- To get a broad perspective on the multidisciplinary process of the clinical development of medical products and to understand how different research areas relate to each other.

1.3. State of the Art of the Pharmaceutical R&D Process and the R&D in Neurology

Over the past few years, pharmaceutical and biopharmaceutical companies have played a major role as drivers of significant medical innovation (7–9). The

research-based pharmaceutical industry applies the most up-to-date technology and scientific knowledge to discover, develop and bring to clinical use new medicinal products that significantly increase patient survival rates and life expectancy, delay disease progression and improve quality of life (7–9).

1.3.1. The Pharmaceutical R&D Process: Overview, Challenges and Trends

Discovering and developing new drugs is a complex and long-term process that consists of several stages and involves various players (8,10). The pharmaceutical R&D (Figure 3) begins with drug discovery followed by preclinical drug development, which includes *in vitro* and *in vivo* tests to assess the pharmacokinetic and toxicological properties of compounds, in order to obtain initial proof of safety and effectiveness (8,10). Compounds that demonstrate attractive therapeutic, pharmacological and toxicity properties, usually 5 or fewer from an original pool that may total 10,000, are subject to three stages of clinical trials (Phase I, II and III) to test their safety and efficacy in humans (8,10). After extensive testing and study, a candidate drug is submitted for regulatory approval (8,10). If approved, post-marketing research and monitoring ensues to gather information on the drug's efficacy in specific patient subgroups and any side effects associated with long-term use (8,10).

Figure 3. The current pharmaceutical R&D process. Adapted from (10).

The task of discovering and developing safe and effective drugs is a risky business (11). Recent studies show that the R&D process is a lengthy process, with an average of 7.2 years to bring a medicine from the beginning of the clinical phase to regulatory approval (11). Also, the likelihood that a compound entering clinical testing will reach the marketplace is estimated to be less than 16% (11). These two factors, long development times and low success rates, along with the high volume of resources required, are translated into very high drug development costs, which were recently estimated to be $2.6 billion (8,12). Therefore, it is easy to understand that the R&D process, as described, is unsustainable.

The recognition of this unsustainability has resulted in the proposal of a new model, with the purpose of improving the R&D productivity (13). The new R&D model aims to establish a drug development process that generates an iterative knowledge on

the relationship between the therapeutic approach and disease pathophysiology, allowing for a continuous improvement of the medicine throughout development (13). This approach is focused in the obtainment of a holistic understanding of the pathophysiology of the disease before starting the clinical phase of the development and in the reduction of the uncertainty on the safety and efficacy profile of the medicine before the expensive later development stages (Phase II and Phase III), through the establishment of proof-of-concept trials (13). These trials allow to determine whether a treatment is likely to be efficacious for a given indication and thus whether it is worth investing the financial resources, time and participant exposure necessary for a confirmatory trial of that intervention (13).

This paradigm shift will be facilitated by the use of adaptive clinical trial designs, which can make the R&D process more flexible and efficient, reducing development costs and time and increasing the probability of success (13). Another important tool in this new R&D model is the use of biomarkers (13,14). Indeed, biomarkers can be used to stratify patient populations with specific disease subtypes to better define the study population of each new medicine and, thus, reducing the number and size of clinical trials required to get regulatory approval (13,14). Moreover, the use of surrogate biomarkers, often considered as replacement for clinically meaningful endpoints, may dramatically shorten the time necessary for critical go/no go decisions in clinical development, as clinically meaningful endpoints may take years to evaluate (13,14).

Like biomarkers, new technologies will be crucial for this new R&D process (13,14). The technological advances will allow pharmaceutical companies to improve the ability to predict a new drug's efficacy and safety in new patient populations (13,14). New technologies will also create the possibility of pharmaceutical companies to monitor patients on a real-time basis and outside the clinical setting, in order to gain a more deep understanding on the course of diseases, and will increase the capability of companies to align and integrate internal information with public data sources, resulting in a greater amount of information available (13,14).

1.3.2. The R&D Process in Neurological Diseases

In developing new drugs for neurological diseases, the pharmaceutical industry faces several challenges related to both disease state and conducting clinical trials (15).

Currently, and despite the great advances in scientific knowledge over the last years, there is still a lack of information and understanding on the mechanisms of neurological diseases, which difficults the identification and/or development of novel

mechanisms of action for drugs and the evaluation of their effects (15). Neurological diseases also lack predictive animal models, increasing the uncertainty throughout the R&D process, and precise measures of efficacy and safety, which compromises the assessment of the real effect of drugs (15).

With regard to the conduction of clinical trials, neurological conditions are characterized by an increased difficulty in recruiting and retaining eligible patients (15). On one hand, neurological conditions are associated with cognitive and physical impairment, making it difficult to perform the required procedures, including the obtainment of informed consent (15). On the other hand, clinical trials on neurological indications have very restrictive inclusion criteria and require longer time periods to demonstrate efficacy, due to the slowly progression of diseases (15).

As a result, neurological disorders have longer clinical development timelines compared to the majority of therapeutic classes (16). In fact, the average time required to perform phase II and III clinical trials increases from 6.1 years in the majority of therapeutic classes to 8.1 years in neurological diseases (16). Additionally, the average time to get regulatory approval increases in neurological disorders – approximately 1.9 years compared with an average of 1.2 years for the majority of therapeutic classes (16). Therefore, without considering the time for discovering and perform preclinical tests, it takes around 9 years to bring a new medicine for neurological diseases to the market (11). Besides the longer clinical development timelines, the chance of compounds for neurological diseases succeeding in phase III clinical trials decrease from 66% to 46% (16). Also, only 8% of the drugs that initiate the development phase receive regulatory approval (11,16).

The comparison between the metrics in the R&D process in neurological disorders and non-neurological disorders is represented in Figure 4.

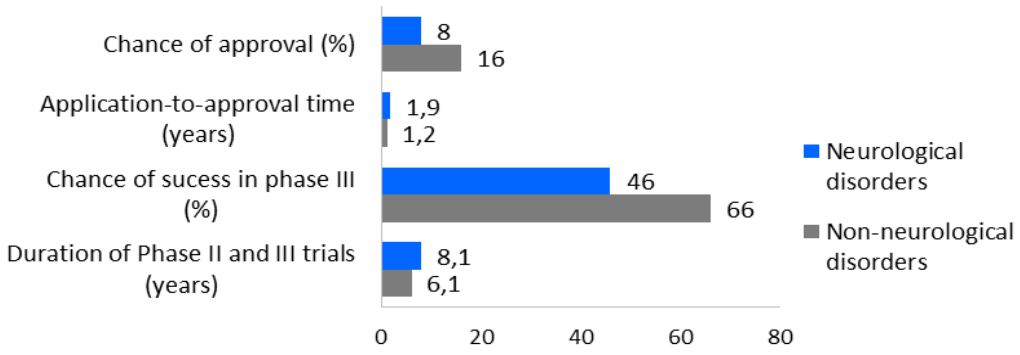

Figure 4. Comparison between R&D metrics in neurological disorders and non-neurological disorders. Adapted from (11,16).

Despite the challenges of developing drugs for neurological disorders, the rewards of bringing neuropharmacologic agents to the market can overcome the risks (16). Neurological disorders significantly outnumber diseases in other therapeutic areas, with more than 600 known conditions affecting the nervous system and with a growing incidence as a result of the aging of the population, and are associated with higher treatment and loss of productivity costs (16). These factors have contributed to encourage the pharmaceutical industry to keep investing in neurological disorders and develop new medicines that work more precisely and more effectively (16). According to a report released by the Pharmaceutical Research and Manufacturers of America, biopharmaceutical research companies are currently developing 420 medicines for patients suffering from neurological disorders, including epilepsy, Alzheimer's disease, multiple sclerosis and Parkinson's disease (17).

1.3.3. Trends and Directions in CNS Drug Development

Pharmaceutical companies are shifting the traditional R&D process for CNS disorders to a process with a higher focus on risk-lowering activities, such as cost-diluting partnerships, increased in licensing and Mergers & Acquisitions activities, and a heavier focus on preventing failures at earlier stages of the development, through improved *in silico* modelling (16).

Over the last years, the vast majority of the neuropharmaceutical development has been conducted on a partnership or collaboration basis, with CNS licensing deals being responsible for 14% of all pharma licensing deals in 2012 and for 15% in the first half of 2013 (16). Also, the pharmaceutical industry has been focusing in settle cooperation and collaboration agreements with academic experts to promote basic research in CNS disorders (16). In 2010, the UCB-Pharma established a research alliance with the Harvard University where the company provided up to $6 million, over two years, to fund innovative research projects with potential for the development of new therapeutic modalities for CNS conditions, led by Harvard scientists (18). More recently, Teva Pharmaceutical Industries LTD invested $15 million into more than 50 CNS research projects at universities across Israel seeking for next-generation treatments for its pipeline (16).

Like pharmaceutical industry, regulatory authorities are also supporting collaborative research projects and building networks of industrial and academic experts in order to foster the development of new innovative drugs for CNS indications (19).

The Innovative Medicines Initiative (IMI) is a public-private initiative of the European Commission (EC) and the European Federation of Pharmaceutical Industries and Associations that aims to improve health by speeding up the development of and patient access to innovative medicines, focusing on areas where there is an unmet medical or social need (19). One of the main focus of IMI was the improvement of drug R&D in CNS disorders through implementation and support of specific projects (19).

In its first phase, from 2008 to 2013, for CNS disorders, this initiative implemented and funded projects that addressed the identification and validation of pre-symptomatic and surrogate markers for disease progression and the development of model systems that were more predictive of the clinical efficacy of new drugs, and projects that aimed to gain a better understanding of disease mechanisms at systems level (20).

For its second phase, period between 2014 and 2020, IMI is intended to support projects aimed at identifying and validating novel targets for prevention and slowing of disease, identifying/developing biomarkers, and developing non-invasive methodologies for assessing disease progression and drug efficacy and safety (21). Other projects supported in this second phase are those that adopt innovative clinical trial paradigms, develop methodologies to demonstrate impact of disease and resultant benefit of treatments, and develop better formulations and delivery methods to support improved adherence to medicines (21).

Besides IMI, there are several other initiatives, such as the European Union Joint Programme – Neurodegenerative Disease Research and the Network of Centres of Excellence in Neurodegeneration, that aim to increase coordinated investment and to build collaborative research activity in neurodegenerative diseases to accelerate the scientific knowledge and the development of new tools for identifying and treating neurodegenerative diseases, as well as to improve social assistance for patients (22,23).

1.3.4. Clinical Trials

Clinical trials are research studies intended to answer scientific questions and find better ways to treat or prevent diseases (24). According to the International Conference on Harmonization (ICH) GCP E6 guidance, a clinical trial is “any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s),

and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" (25).

Although the definition of clinical trial had been associated with the study of drugs, currently it is broadly used to include other forms of intervention besides drugs such as surgical procedures, radiological procedures, medical devices, behavioural treatments, process-of-care changes, preventive care, etc (24,26).

1.3.4.1. Types of Clinical Trials

Assessing the efficacy and safety of a new intervention often requires several different clinical trials (27). Typically, the testing in humans is described as consisting of four temporal phases (Phase I-IV) (27). However, one type of trial may occur in more than one phase and a classification based on the objective of the trial is more adequate (27).

Each phase of clinical testing has specific and differing requirements for patient population, objectives, inclusion/exclusion criteria, design features, and expected outcomes (28). Ideally, clinical testing is carried out in a logical, step-wise procedure with results from prior clinical trials being used to support and plan trials performed later in the development process (27). The clinical testing progress from trials designed to evaluate short-term safety and tolerability (Phase I), to trials aimed at defining dose-response relationships (Phase II) and at determining the efficacy and safety with the dose(s) of interest (Phase III) (28).

- **Phase I (Human pharmacology studies)**

Phase I studies are the initial phase of testing in humans and are primarily designed to assess the tolerability and safety of the drug (27). Usually, phase I studies use dose escalation designs to determine the maximum tolerated dose (28). Additionally, data on pharmacokinetics and pharmacodynamics and drug metabolism, interactions and activity are collected (27). These type of studies include about 20 to 100 healthy volunteers without confounding diseases or concurrent medications (28). However, when there are toxicity limitations, phase I studies are performed in volunteers with the disease or condition of interest (27,28).

This phase of testing takes approximately 1.5 years to complete (28).

- **Phase II (Therapeutic exploratory studies)**

Phase II studies are performed with the intent of exploring use in the target indication in patients with the condition or disease of interest (27). Additionally, phase II studies also help to determine the common short-term side effects and risks associated

with the drug (27). These studies are well controlled and closely monitored and use a relatively homogeneous population, with very tight inclusion and exclusion criteria, of several hundred (100 to 300) patients (28). The first clinical trials of this phase of testing may have a variety of designs (27). However the subsequent trials are randomized, controlled and blinded (27).

A major focus of this phase of testing is to estimate dosage and/or dosage scheme for subsequent trials and provide basis to define the design, endpoints and methods for confirmatory studies (28).

Usually, phase II studies take around 2 years to complete (28).

- **Phase III (Therapeutic confirmatory studies)**

Phase III studies aim to confirm the efficacy of the drug in the target indication and establish drug safety profile and dose–response relationship (27). The information gathered in these studies constitutes the basis for assessing the benefit-risk relationship of the drug, in order to get regulatory approval for marketing (27,28). The typical study design used in phase III trials is randomized and placebo-controlled, but an active comparator control group can be considered (28). The patient population of phase III studies is more heterogeneous than that studied in phase II and, usually, includes 1,000-3,000 patients distributed over many sites (28).

Studies in phase III usually require about 2.5 years to complete (28). However, in some cases, this timeline can be extended to 5 years (28).

- **Phase IV (Therapeutic use studies)**

Phase IV studies are conducted after a drug has been approved for marketing and include only studies performed in the approved indication(s) (27). These studies aim to monitor a drug's long-term safety and efficacy, in order to refine the understanding on the benefit–risk relationship and impact on a patient's quality of life, to identify less common adverse reactions and refine dosing recommendations (27). Over the past few years, these type of studies have also been used to determine the cost-effectiveness of a drug over other drugs already on the market or new ones (28).

Studies in phase IV have more simple study designs and are often very large (28).

1.3.4.2. Regulatory Framework

Considering the ethical and safety concerns regarding study participants, the importance of the information gathered and the multiplicity of stakeholders involved, it is easy to understand that clinical trials are a highly regulated activity (29).

Over the last years, several directives, regulations, guidance documents and ethical standards have been published to protect the rights and integrity of patients and study volunteers and to guarantee the high quality of the data produced/collected (29). Despite the existing amount of legislation and guidance documents concerning the conduction of clinical trials, the most important ones are the following:

- Declaration of Helsinki, which specifies a series of ethical principles for medical research involving human subjects, including research on identifiable human material and data, in order to protect research participants (30). Although it has no legal status, it is recognized, on a global scale, as the code of conduct of medical research on humans and is referenced in nearly all clinical trial protocols submitted to ethics committees;
- ICH GCP E6 guidance, which outlines a set of principles that aim to ensure the rights, safety and well-being of research subjects, and the high quality and credibility of the clinical data obtained, by defining, in detail, the responsibilities and obligations of all parties engaged and by defining standards for designing and conducting research and recording and reporting data (25);
- Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001, which is also known as the Clinical Trial Directive and aims to harmonize the research activity in the European Community by providing a framework that sets out how clinical trials must be conducted to ensure the protection of the trial participants and the overall quality of the trial (31). Initially, this directive was transposed into the Portuguese national law by Decree-Law 46/2004 of August 19th. More recently, this Decree-Law was repealed by Decree-Law 21/2014 of April 16th (32);
- Commission Directive 2005/28/EC of 8 April 2005, or the GCP Directive, which complements the Directive 2001/20/EC by setting out the principles and guidelines of GCP applicable to clinical trials and the requirements for authorization of the manufacturing or importation of investigation medicinal products (33). In the Portuguese legislation, the principles set out in this directive are specified in Decree-Law 102/2007 of April 2nd (34);
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995, also known as the Data Protection Directive, which sets up a

regulatory framework that ensures the protection for the privacy of individuals by defining limits on the collection and use of personal data (35). This directive was transposed to national law by Law No 67/98 and by Deliberation nº333/2007 (36,37);

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014, which repeals the Directive 2001/20/EC and aims to make clinical trials simpler to set up, mainly through the establishment of a centralized system for approving clinical trials, and more transparent in reporting their results, including negative findings (38). This Regulation also intends to eliminate the disparity adopted by Member States in transposing the Directive 2001/20/EC (38). Although it has entered into force on 16 June 2014, it will only apply starting from 28 May 2016 (39).

1.3.4.3. Clinical Trials in Portugal

The number of clinical trials submitted to INFARMED between 2006 and 2012 show a decrease of 26%, from 160 to 118 trials (Figure 5), making Portugal one of the countries of the Western Europe with the lowest rate of clinical trials per million inhabitants (40). In the last three years (2012, 2013 and 2014), there seems to be a tendency towards the stabilization of the number of clinical trials submitted to INFARMED (Figure 5) (41).

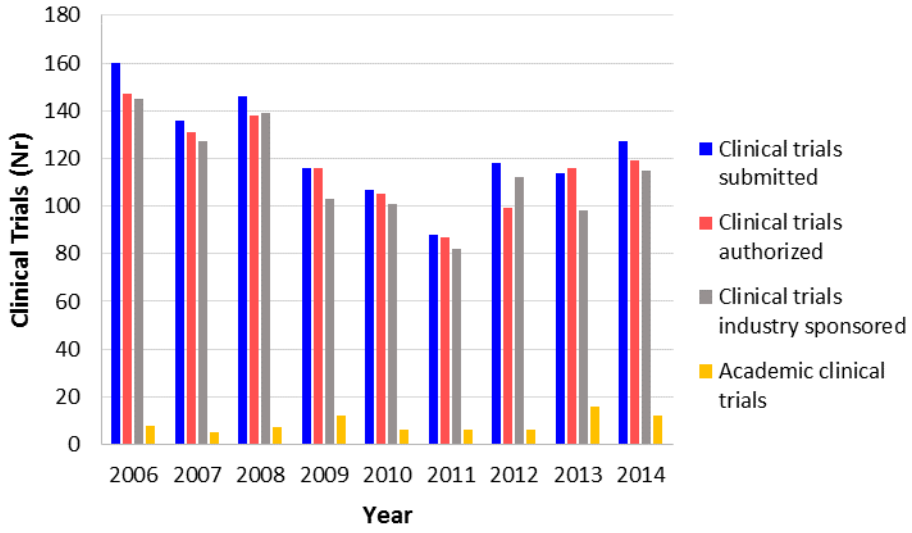

Figure 5. Number of clinical trials submitted to and approved by INFARMED and sponsored by the pharmaceutical industry and by academic institutions, from 2006 to 2014, in Portugal. Adapted from (41).

According to a study released on 2013 on the clinical trials activity in Portugal, the large majority of the clinical trials conducted were sponsored by the pharmaceutical industry (40). Data from 2012 show that 112 of the 118 trials submitted to INFARMED were sponsored by pharmaceutical companies, with only 6 trials being submitted by academic institutions (Figure 5) (41), which represents a very low expression, especially considering other Western European countries where academic trials represent about a quarter of the total number of trials conducted (40). This tendency is supported by the latest statistics on the sponsorship of the clinical trials submitted to INFARMED (Figure 5) (41). Also, phase III and IV clinical trials were responsible for 80% of all trials conducted in Portugal in the last years, with phase III trials alone being responsible for 68% of the trials approved in 2012 (40). In what concerns phase I clinical trials, these had almost no representation, with only 8 trials approved between 2009 and 2012 and with only 10 trials submitted in 2013 (41).

Regarding the number of patients enrolled in clinical trials, Portugal had also been far below the other countries of the European Economic Area (40). Data from a report released by the EMA on the patient recruitment and geographical location of investigator sites of clinical trials submitted to the Agency, between 2005 and 2011, Portugal included an average of 23 patients per trial, a small number compared to countries like Hungary and Czech Republic (82 and 107 patients, respectively), which have a population comparable to that of Portugal (42).

The reduced number of clinical trials conducted in Portugal over the last years is revealing of a progressive loss of competitiveness of the country (40). The lack of interest from sponsors to conduct clinical trials in Portugal is harmful to the country and its economy, as it prevents the access of the population to new and innovative therapies, the adoption of best practices in monitoring of patients, the improvement of supportive care and cost savings with healthcare (40).

The recognition of this worrying reality resulted in the definition of a new strategy, by the Ministry of Health, to promote clinical research and to increase competitiveness and transparency in this sector (43). On April 16th of 2014, the Law 21/2014 was approved (32). This Law represents a change in the legislation in force by establishing a more comprehensive and harmonized legal framework, covering not only clinical trials with medicinal products but also studies with medical devices, cosmetics, food supplements and all kind of observational studies, and by defining new timelines for approval of clinical trials (32), which have been identified as one of the most limiting factors of this activity in Portugal (40). Indeed, this Law establishes more competitive timelines with a considerable reduction in the time provided to all parties involved in the approval process to take a position on the conduction of the trial (32).

The Law 21/2014 also establishes the creation of an electronic platform for registration of clinical trials, the *Registo Nacional de Estudos Clínicos* (National Clinical Trial Register) (32). This platform aims to promote the interaction between the different stakeholders in clinical research, facilitating and encouraging the development of high quality research, and the dissemination of the clinical research activity (32). Furthermore, the Law defines the creation of the *Rede Nacional de Comissões de Ética para a Saúde* (National Ethics Committees Network) promoting harmonization on the assessment of clinical trial applications and the mutual recognition between national ethics committees (32).

Besides the approval of the new Law, two other initiatives are under development by the Ministry of Health, in order to increase the clinical trials activity in Portugal (43). The first one is the revision of the criteria for purposes of career progression, in a first stage, for physicians who assume the role of investigators and, in a later stage, for other professionals involved in clinical research (43). The other initiative is the establishment of a research fund, sustained by the Ministry, which aims to ensure suitable conditions for projects by initiative of investigators (43).

1.3.4.4. Clinical Trials in Neurology

Clinical trials involving CNS disorders are among the most difficult ones to set up and run (16). As mentioned above, clinical trials in neurology are associated with subject recruitment and retention problems (16). In fact, the available diagnosis techniques for neurologic disorders are very poor and, in the vast majority, outdated considering the recent technological advances, resulting in delayed diagnosis (16). Therefore, patients often fail to meet inclusion criteria due to the advanced stage of diseases (16).

The recruitment of patients for clinical trials is also difficult due to the restrictive inclusion criteria, the informed-consent process and the assessment procedures (15). Neurological diseases are associated with cognitive impairment, compromising the ability to make decisions such as participation in clinical trials, which difficulties the obtainment of informed consent from patients, and the ability to comply with the study procedures and with the study medication (15). Along with the common impaired cognitive abilities, the physical immobility of patients with CNS disorders is also a major hurdle in clinical trials, mainly in those that require long periods of time (15).

The assessment of the effect and safety of drugs for CNS indications in clinical trials often requires frequent hospital visits and the use of exhaustive evaluation processes/tools, which can restrict patient compliance or make subjects to withdraw consent to participate in the trial (15). This difficulty in retaining eligible patients along

with the difficulty in recruiting patients can result in small sample sizes, compromising the assessment of the effect of the drug (15).

Besides the frequent small sample sizes of CNS trials, the difficulty in determining the effect of CNS drugs is further exacerbated by relatively poor diagnosis techniques, which do not allow the distinction between different stages of disease (16). It is usual to have a cohort of patients in a clinical trial among which disease progression would vary drastically, making it difficult to assessing the effect of the drug (16). Another hindrance in determining the effect of the experimental drug in CNS trials is the placebo effect (16). Currently, the vast majority of clinical assessments is based in neuropsychological scales, which can be influenced by confounding cognitive, mood or personality changes of patients caused by the belief that they are being treated (16).

Although neurological conditions represent a substantial clinical challenge, between 2005 and 2010, the number of clinical trials registered in the ClinicalTrials.gov database in CNS disorders was the highest among the non-oncology group of therapeutic areas, with 7,751 trials (44). In December 2011, there were 603 phase I-III clinical trials in neurologic diseases filed with the Food and Drug Administration, with a higher number of earlier-phase trials (256 phase I, 273 phase II and 74 phase III trials) (45). Nevertheless, neurology was the third most common therapeutic area in Phase III clinical trials, after cancer and infections (45).

Considering the number of clinical trials submitted to INFARMED between 2006 and 2014, CNS disorders accounted for one of the therapeutic areas with the highest number of clinical trials submitted (Figure 6) (41).

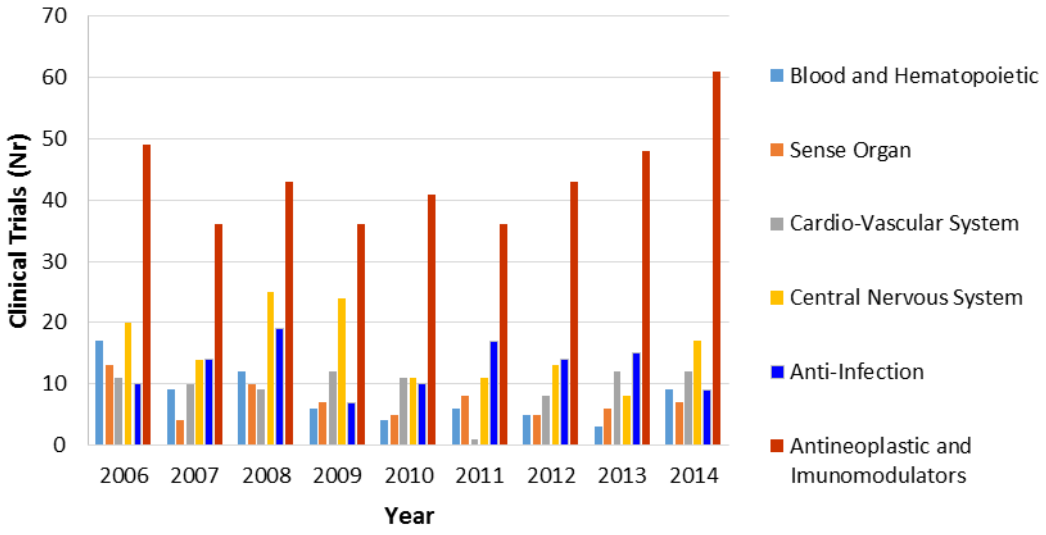

Figure 6. Number of clinical trials submitted to INFARMED from 2006 to 2014, by therapeutic area. Adapted from (41).

The numbers presented corroborate that neurological diseases have been a therapeutic area greatly focused on by pharmaceutical companies (44).

2. On-the-Job Training

During my curricular training, I had the opportunity of interacting and collaborating with different research areas in the host institution. In this chapter, I present a detailed description of all the activities performed during this 10-month period. The training received is divided into generic training and specific training, according to the level of qualification acquired. The generic training corresponds to the activities developed in the context of data management, pharmacovigilance and medical writing and the specific training describes the activities developed as trainee in clinical trials coordination.

The first two months of the training were carried out in the *Sub-Unidade de Bioestatística e Metodologia* where I was able to participate in several activities, such as management of clinical databases for statistical analysis and in the development of documents in the context of data management activities, mainly quality control of clinical data.

After my experience in the *Sub-Unidade de Bioestatística e Metodologia*, I had the opportunity of collaborating with the URFLVT. During this collaboration I was able to acquire knowledge and skills in the area of pharmacovigilance and to gain qualification for the daily activities of this unit, mainly for the reception, validation and processing of spontaneous reports of ADRs.

For the last six months of the training I went to the CIC where I learned to perform the daily activities of a CRC, from the preparation and conduction of study visits to the completion of Case Report Forms (CRFs) and resolution of queries, including all the logistical aspects related to the conduction of clinical trials.

Besides the clinical trials coordination, data management and pharmacovigilance activities performed, I also had the opportunity to participate in a series of parallel projects in the host institution, mainly writing of scientific papers.

2.1. Generic Training

During my curricular training I had the opportunity of collaborating and participate in several activities besides the coordination of clinical trials. The purpose of the developed activities was to get a broad perspective on the multidisciplinary process of the clinical development of medical products and health research activities, as well as to understand how different research areas relate to each other. These activities are schematically represented in Figure 7 and are fully described in the following pages.

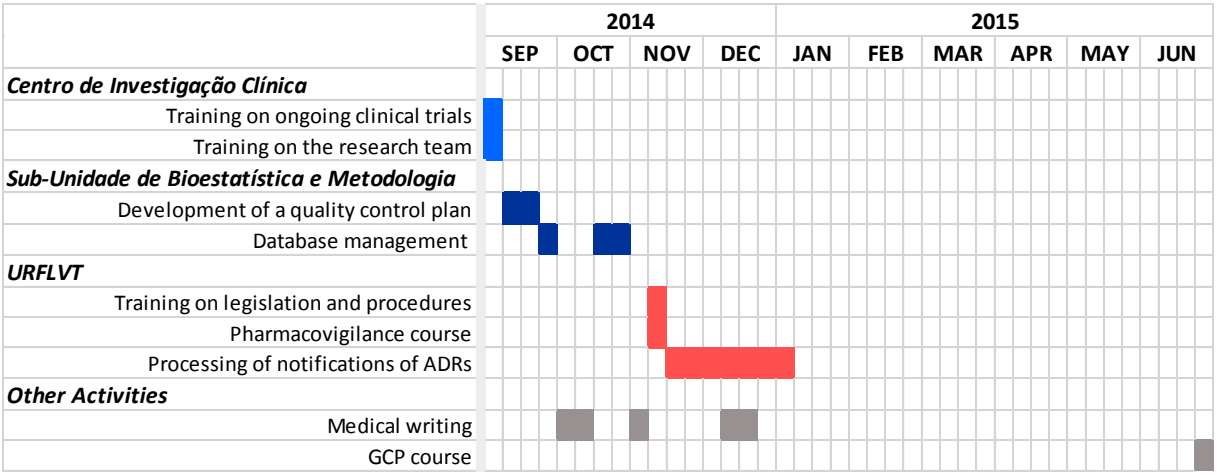

Figure 7. Timeline of the main activities developed in the generic training.

2.1.1. Training on the Ongoing Studies and Organization of the CIC

During my first week of the training, I went to the CIC where I received training on the ongoing clinical trials and on the research team of the sub-unit. The main purpose of this training introduction was to prepare me to start the specific activities of clinical trials coordination.

2.1.1.1. Ongoing Clinical Trials

The study protocol describes how a clinical trial will be conducted and ensures the safety of the trial participants and the integrity of the data collected (25). The training on the study protocol is given to the research team in the investigators meeting and in the site initiation visit and ensures protocol compliance.

When I first arrived at CIC, to obtain a knowledge on the ongoing trials, I did a comprehensive reading of the study protocols and complemented the knowledge on them by clarifying the doubts with the CRCs of the CIC. After that, I was able to actively participate on the clinical trials.

2.1.1.2. The Research Team

The clinical research activity requires teams dedicated to clinical research and qualified according to the standards of GCP and to the applicable legal and quality requirements. The research team, comprises any person delegated by the research team leader to have operational charge of any specific procedure of the trial.

During my first week in CIC I was introduced to all members of the research team of the sub-unit and instructed regarding the clinical trials and the specific roles delegated to each member. This was important to facilitate the management of the different studies.

2.1.2. Data Management Activities

My curricular training in the *Sub-Unidade de Bioestatística e Metodologia* was focused on quality control activities and organization of databases of clinical data for statistical analysis. The purpose of this part of the training was to acquire basic knowledge and skills in clinical data management.

2.1.2.1. Quality Control Plan

Within the scope of quality control activities, the *Sub-Unidade de Bioestatística e Metodologia* is responsible for editing, cleaning, verifying, cross-checking and validating data collected in clinical studies, in order to ensure their reliability and credibility.

During my training in this research sub-unit, I was challenged to collaborate in the development of a quality control plan where I had to identify the methodologies to be used for checking data completeness, integrity and consistency, and for detecting double data entry, missing values, out-of-range values, anomalous values and errors, in order to validate data for statistical analysis. This activity was carried out within the scope of the Enroll-HD study, a worldwide observational study for Huntington's disease that aims to increase the knowledge on the biology of the disease to enable clinical research for improving clinical care of people with Huntington's disease, through collection of clinical data and biological samples (46).

2.1.2.2. Database Management

Usually, the data collected in clinical studies requires to first be processed so that the statistical analysis can be made. In this context, during my training in the *Sub-Unidade de Bioestatística e Metodologia*, I had to organize two different databases.

One of the databases was intended to gather data collected in the project Sense-Park, a European funded initiative that aims to develop a series of technical devices that allow the continuous assessment of motor and non-motor symptoms (sleep, tremor, rigidity, stiffness, walking, gait) for an objective and precise analysis and measurement of Parkinson's disease (47). For this purpose, I converted the original records on the clinical domains (motor and non-motor symptoms) collected with the devices into means and medians and entered the values into a database, in a way that data could be directly used by statistical software.

The other database was intended to organize data on ADRs for which the suspected drugs were thrombolytics, anticoagulants and/or antiplatelet aggregation drugs, for statistical analysis. In this database I had to disaggregate some variables

and to calculate others, such as body mass index. This database was developed within the scope of a personal project of an investigator of the UFC.

2.1.2.3. Other Activities

Besides the quality control and database management activities, I was able to assist in several other secondary activities. These included search the internet for best practices for data cut release and for methods for de-identification of protected health information, both within the scope of the Enroll-HD study, adaptation of a manuscript to the formatting requirements of the Journal of Parkinson's Disease, and collaboration in the submission of a project to a research grant sponsored by the *Santa Casa da Misericórdia de Lisboa* (Holy House of Mercy of Lisbon).

2.1.3. Pharmacovigilance Activities

My curricular training in the URFLVT was divided into two main components: 1) acquisition of basic knowledge on pharmacovigilance and its regulatory framework, presentation of the SNF and of the URFLVT, and understanding of the URFLVT quality management system and workflow, and 2) reception, validation and processing of spontaneous reports of ADRs. The main objective of this part of the training was to gain knowledge on the structure of the unit, its mission, requirements, vision and activities, and to gain qualification to perform the daily activities of a regional pharmacovigilance unit.

2.1.3.1. Regulatory Framework

Pharmacovigilance is governed by several regulations, directives, guidelines, and standards that ensure the accurate conduction of pharmacovigilance activities. In the first week of my curricular training at URFLVT, I was invited to read the main pharmacovigilance regulatory documents, in order to better understand the specific requirements of the URFLVT, and then, to properly carry out the training activities. These documents included:

- Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 and Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010, which lay down the community procedures for the pharmacovigilance of medicinal products for human use within the EU (48,49);

- Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012, which complements the 2010 pharmacovigilance legislation by providing more technical details that have to be observed by marketing authorization holders, national competent authorities and EMA in the daily practice of applying the new legislation (50);
- Decree-Law 20/2013 of 14 February 2013, which transposes into national law the Directive 2010/84/EU (51);
- Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012, which clarifies and strengthens the procedures used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines (52);
- Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012, which defines a list of medicinal products that are subject to additional monitoring (53);
- Good Pharmacovigilance Practices – Module VI, which presents a set of measures drawn up to facilitate the management and reporting of adverse reactions to medicinal products (54).

2.1.3.2. Quality Manual and Procedures

Since August 2013, the URFLVT has implemented a quality management system, in accordance with the European version of the International Organization for Standardization 9001:2008, to consistently accomplish its objectives and to ensure compliance with all regulatory requirements applicable to its activity. One of the key components of the URFLVT quality management system is the quality manual that contains the quality policy and goals of the unit, as well as a detailed description of its quality control system, which includes staff roles, procedures and interactions between procedures, systems and any other resources required to perform specific activities.

Before I start performing any activity, I read the URFLVT quality manual, mainly to become aware of the specific steps to follow to carry out the different pharmacovigilance activities – working instructions. Considering the activities to be undertaken during the training, I focused on the working instructions related to the reception and validation of ADRs, preparation of the initial notification report, request for additional information on notifications and preparation of the follow-up report.

2.1.3.3. Pharmacovigilance Course

During my first week in the URFLVT, I had the opportunity to attend an intensive course of 16 hours on pharmacovigilance, organized by the URFLVT. The course provided an overview on the mechanisms of ADRs, methods for drug safety monitoring, risk-benefit assessment of drugs, causality assessment of ADRs and pharmacoepidemiology studies. The course also gave a brief insight on the most common ADRs for the different systems of the human body, with a description of the mechanisms that are involved and identification of the most likely causative drugs.

2.1.3.4. Reception, Validation and Processing of Spontaneous Reports of ADRs

The main activity performed during my curricular training in the URFLVT was the reception, validation and processing of spontaneous reports of ADRs. A spontaneous report is an unsolicited communication by healthcare professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (54). Spontaneous reports of ADRs are the main source of data on the safety of medicines used by the SNF (55). The major value of spontaneous report systems lies in the early detection of possible drug safety problems that have not yet been identified (56). Also, spontaneous reports allow for large scale and continuous monitoring of the safety of drugs and the identification of risk groups and serious and/or rare adverse effects (56).

During the second half of 2014, which includes the period I was in the URFLVT, 422 spontaneous reports of ADRs were received, validated and processed. The reception, validation and processing of spontaneous reports of ADRs in the URFLVT is done according to specific written procedures. During my training, I received, validated and processed spontaneous reports of ADRs, always under the close supervision of the two pharmaceuticals of the unit. Following, I present a description of the process used to receive, validate and process spontaneous reports of ADRs.

- ***Reception and Validation of Spontaneous Reports of ADRs***

When a spontaneous report of ADR was received in the URFLVT, the first step was to validate the report, which consisted in verifying that: (1) the notification belonged to the area of activity of the URFLVT; (2) the report did not correspond to a duplicate of a previously received one; (3) the suspected drug was actually a drug; and (4) the four minimum criteria for acceptance of a report (one or more identifiable reporter(s), one single identifiable patient characterized by initials, patient identification

number, date of birth, age, age group or gender, one or more suspected medicinal product(s) and one or more suspected ADR(s)) were present. If all criteria were met, I signed and dated the report with the date of the reception and assigned a code number to indicate that the report was validated. When a report did not meet the minimum criteria, especially if it corresponded to a serious and/or unexpected ADR, I made attempts to get all necessary information from the reporter or other available sources.

- ***Processing of Spontaneous Reports of ADRs***

The processing of spontaneous reports of ADRs was made within a maximum of 7 days following their reception and validation. In order to avoid deviations, once the report was considered valid, I set a time limit in the calendar for completing the processing of the report.

After validation, I classified the ADR as described/non-described, according to the information in the summary of product characteristics, and, if not provided by the reporter, as serious/non-serious, if the ADR was present in the Important Medical Event Terms list and/or in the Council for International Organizations of Medical Sciences list. These two documents contain a set of ADRs that must always be considered as serious. Also, if the reporter classified the ADR as non-serious, I made a search in the mentioned lists to ensure that the ADR was not required to be considered as serious.

Besides classifying the ADR, I had to code it to terms in the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA is a standardized set of medical terminology used for registration, documentation and safety monitoring of medical products, that was developed to facilitate sharing of regulatory information (57). After classifying and coding the ADR, I introduced the information present in the report on a platform – *Portal de Reações Adversas a Medicamentos* (*Portal RAM*, Portal of Adverse Drug Reactions) – , managed by INFARMED, that enables the collection of information on suspected ADRs occurred in Portugal.

After entering the data of the spontaneous report in *Portal RAM*, I contacted the reporter to obtain additional information relevant for the scientific evaluation of the case. This information, together with the data of the report, was then used to write a narrative of the case, in which I described the patient characteristics, therapy details, medical history, diagnosis, ADR and its outcomes, relevant laboratory evidence and any other relevant information. This narrative was also introduced in *Portal RAM*.

The information introduced in *Portal RAM* was always checked by one of the two pharmaceuticals of the unit to verify that the ADR was correctly classified and coded and the information was correctly introduced.

The last step of the processing of spontaneous reports was the causality assessment, which defined the probable causal relationship between the suspected medicinal product and the ADR. The causality assessment was done by the steering committee, within 30 days after the validation of the spontaneous report. Once the assessment was done, I prepared the causality letter identifying the causal relationship attributed to the case to send to the reporter and wrote the causality report and attached it in *Portal RAM*.

When the information of the spontaneous report was incomplete, I made a follow-up contact with the reporter, usually one month later, to obtain new information that has arisen and did a follow-up report, which complemented the narrative of the case.

All the information introduced in the Portal RAM was sent to the SNF database SVIG (*Sistema de VIGilância,* Vigilance System). This database gathers all spontaneous reports from the different regional pharmacovigilance units.

2.1.4. Medical Writing Activities

During my training in the *Sub-Unidade de Bioestatística e Metodologia*, I had the opportunity to collaborate in other projects outside the scope of activities of the sub-unit, most of them related to systematic reviews and meta-analysis on cardiovascular topics.

2.1.4.1. The impact of systematic reviews with meta-analysis on the European Society of Cardiology's guidelines

This was a study carried out to evaluate different methodologies used for identification of systematic reviews and/or meta-analysis cited in the 2001, 2006, 2010 and 2012 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation.

The identification of the systematic reviews and meta-analysis was performed using four different methods: 1) a two member manual screening of the references of each guideline, 2) a text-mining approach using Adobe Software, 3) a text-mining approach using EndNote, and 4) a text-mining approach using both Adobe Software and EndNote. As my knowledge and experience regarding systematic reviews and meta-analysis was limited, I did not perform the manual approach.

In the approach using the Adobe Software, I used the search feature, with predefined keywords, on the references section of each guideline to identify the systematic reviews and meta-analysis, by their title. In the approach using EndNote,

first I imported the references of each guideline, including title and abstract, from the Web of Science to EndNote and then I searched the downloaded references using the search filters, also with predefined words, for paper title (first) and abstract (second).

After applying the methodology of the study, I had an active participation in the analyses of the results obtained. Once the study was complete, a scientific paper was written. In the paper, I collaborated in the writing of the discussion section where I reviewed the characteristics and limitations of systematic reviews and meta-analysis.

Although this project was almost concluded, it was suspended since other ideas for papers were deemed more relevant.

2.1.4.2. Risk of substantial intraocular bleeding with non-vitamin K antagonist oral anticoagulants: Systematic Review and Meta-analysis

This was a study aimed at estimating the risk of intraocular bleeding associated with the use of Non-vitamin K Oral Antagonist Anticoagulants (NOACs) through a structured literature review and meta-analysis of phase III randomized controlled trials comparing NOACs with controls, which included active drugs and/or placebo.

In order to identify the intended clinical trials, a search on the Medline and Cochrane Library was performed (inception to November 2014). The reference lists of systematic reviews and of each included study were also searched. After a comprehensive search, 17 studies were included and analyzed to extract data on intraocular bleeding events, using the RevMan 5.3.3 software, to synthesize the measures of effect.

For this study, my contribution was limited to data analysis, which consisted in the identification of the arms (NOAC and control) of each phase III randomized controlled trial included and the total number of patients and intraocular bleeding events in each treatment arm.

The paper that resulted from this study and of which I was designated co-author was published on the JAMA Ophthalmology (58).

2.1.4.3. Risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants: Systematic Review and Meta-analysis

This was a study very similar to the study “Risk of intraocular bleeding with non-vitamin K antagonist oral anticoagulants: Systematic Review and Meta-analysis”. The aim of this study was to evaluate the risk of major gastrointestinal bleeding associated with NOACs, also through a structured literature review and meta-analysis of phase III randomized controlled trials comparing NOACs with controls. For the purpose of this

study, the methodology applied was identical to the methodology applied in the previous one.

In this study, besides data analysis, I was involved in the writing of the study paper in which I described the results of the search and the characteristics of the included studies and made a summary table with the information that was extracted during data analysis.

At the end of my curricular training, this paper was being prepared for submission on the Alimentary Pharmacology & Therapeutics Journal.

2.1.4.4. Risk of hematuria with non-vitamin K antagonist oral anticoagulants: Systematic Review and Meta-analysis

This was a study in line with the previous ones. The aim of this study was to evaluate the risk of hematuria associated with the use of NOACs, comparing the number of events of hematuria in the different treatment groups (NOACs and controls) of the same phase III randomized controlled trials selected for the previous studies.

For this study, as in the previous ones, I collaborated in data analysis, extracting data required to assess the risk of hematuria. Also, I was responsible for writing the introduction of a paper with the results obtained where I reviewed the main advantages of NOACs compared to the anticoagulants used before the introduction of NOACs, in terms of efficacy and safety, and discussed the uncertainty regarding the risk of hematuria for NOACs.

However, this project was not concluded since flaws in the data extraction process, more specifically, in the identification of the hematuria events, were discovered.

2.1.5. Other Activities

2.1.5.1. Journal Club

Every Wednesday, at 8 am, I attended the Journal Club, a meeting carried out by the investigation team of the CIC with the purpose of discussing recent findings in the field of neurology and neurosciences, usually clinical study reports. The discussion focused mainly on considerations on the design of the study, the potential therapeutic applications of the findings, and what prospects these studies could bring to the activities of the unit, amongst other topics.

These morning sessions also served a double purpose, as they allowed for the team to discuss and share some information and problems about the functioning of the

sub-unit and to present and discuss clinical cases, in order to take advantage of the different backgrounds of the members of the team, to make the best clinical decisions.

2.1.5.2. Wednesday Afternoon Meetings

Every two weeks, on Wednesdays afternoon, I attended a meeting, held on the UFC, with all members of the team. These meetings had the purpose of sharing knowledge and perspectives on different topics, such as clinical outcomes, clinical trial methodologies, pharmacovigilance, quality management systems, quality control and de-identification of clinical data, clinical statistical monitoring, data monitoring committees, interim analyses, early stopping in clinical trials and risk management plans.

Another purpose of these meetings was to share the ongoing or future projects of the different sub-units and/or team members to discuss and obtain feedback on the concept, methodology and other important aspects, in order to improve them.

2.1.5.3. Data Entry and Drawing-up of a Database

In parallel with the activities of clinical trials coordination I was invited to collaborate in a project of an investigator from CIC. The project was related to deep brain stimulation for Parkinson's disease and my collaboration consisted in the introduction of clinical data of patients who underwent surgery into a database, according to predefined specifications, for statistical analysis.

Another activity that I have accomplished in parallel with clinical trials coordination was drawing-up of a database with demographics and other relevant data of patients participating in the REGISTRY study, to help in the management of study visits. The REGISTRY is a multi-center, multi-national observational study that focuses on the collection of clinical and biological data from patients with Huntington's disease to provide an extensive repository of data to facilitate studies in this disease (59).

2.1.5.4. Good Clinical Practice Course

At the end of my curricular training in the UFC, I was invited by Professor Joaquim Ferreira to attend a course organized by the unit on GCP to strengthen my knowledge about this theme. The course had a duration of nine hours and focused on the principles of GCP, legislation and regulatory aspects associated with clinical trials, study protocol design, essential documents, responsibilities of the study sponsor, monitor and CRC, safety and Adverse Event (AE) reporting and practical aspects of conducting clinical trials.

2.2. Specific Training

The main activity developed during my curricular training was clinical trials coordination. The role of the CRC is central to the successful conduct of a clinical trial. Many of the responsibilities of the research investigator are primarily the CRC's operational responsibility, ranging from preparing the site for implementation of the clinical trial to managing patient scheduling and follow-up, recording and verifying data in CRFs, ensuring study supplies are properly inventoried, stored and recorded and keeping study files and records.

During my training in clinical trials coordination, which lasted from January 2015 to June 2015, I had the possibility to actively collaborate in almost all clinical trials ongoing in CIC. The clinical trials in which I was able to work are presented in Table 1, as well as the respective study phase and condition under treatment.

Table 1. Clinical trials ongoing in CIC in which I actively collaborated.

Clinical Trial Acronym (EudraCT Number)	**Study Phase**	**Pathology**
EXPAND (2012-003056-36)	III	Secondary Progressive Multiple Sclerosis
PROTEC (2013-001656-35)	IV	Relapse-Remitting Multiple Sclerosis
EPOCH (2011-003151-20)	II / III	Alzheimer's Disease
LEGATO (2014-000418-75)	II	Huntington's Disease
ISIS (2012-001831-30)	II / III	Familial Amyloid Polyneuropathy
ACADIA (2007-003035-22)	III	Parkinson's Disease
MARGARITE ROAD (2013-003390-95)	III	Alzheimer's Disease
ORATORIO (2010-020338-25)	III	Primary Progressive Multiple Sclerosis
BIAL 311 (2009-011135-13)	III	Epilepsy
DUODOPA (2008-001329-33)	III	Parkinson's Disease
SCARLET ROAD (2010-019895-66)	III	Alzheimer's Disease

The activities performed in each of the mentioned trials were in agreement with the enforcement stage of each clinical trial and are summarized in Table 2. In the following sub-sections I discuss the main components of these activities.

Table 2. Study coordination activities performed in the different clinical trials.

Study Visit[1] / Clinical Trial	Screening	Randomization	Treatment	End-of-Treatment	Follow-up
EXPAND			X	X	
PROTEC	X	X	X		
EPOCH	X	X	X		
LEGATO	X	X			
ISIS	X	X	X		
ACADIA			X		
MARGARITE ROAD			X		
ORATORIO			X		
BIAL 311			X		
DUODOPA			X		
SCARLET ROAD					X

[1]Study visits imply preparation and conduction of study visits, eCRF completion, documents management and sample shipping.

2.2.1. Initial Training Activities

At the beginning of my curricular training in the CIC I received training on more logistical aspects of conducting clinical trials to be able to support the CRCs of the sub-unit performing the specific activities of the different trials.

2.2.1.1. The Study Documentation

All information generated in the course of a clinical trial must be recorded, handled and stored, in order to allow the best conduct of the trial and the highest quality of the data produced, and to prove the trial was conducted in accordance with the protocol and all the applicable regulatory and ethical requirements. This information may be filed in the Investigator Site File (ISF) and/or in the patient's file.

2.2.1.1.1. The Investigator Site File

The ISF is a file that is provided to the site at the site initiation visit and contains all the information that the site staff needs to carry out the clinical trial (60). Typically, it contains the investigation protocol and further amendments (when applicable),

investigator's brochure, updated and obsolete versions (if applicable) of the Informed Consent Forms (ICFs), clinical trial approvals, laboratory manual, CRF completion guidelines, delegation and subject logs, curricula of the research staff, training certificates, correspondence, and other documents related to the trial (60).

During my curricular training, I had the opportunity to contact with ISFs from different studies. This allowed me to understand how these files may be organized. After understanding the organization of the ISFs of the clinical trials ongoing in CIC, I archived the documents that arrived at the sub-unit and identified if there was any missing documentation, in order to request it to the study sponsor. Besides archiving documents, I also helped in the completion of the subject recruitment, screening and confidentiality logs, which are documents of the ISF that must always be kept up-to-date.

2.2.1.1.2. The Patient's File

The patient's file is a file containing the demographic and medical information about the patient, as well as all records generated in the course of the trial (60).

Before each study visit, I reviewed the patient's file to resolve any pending issues, such as signature of previous blood analysis reports or clinical evaluations, and to answer clinical queries. After the visit, I archived all the information generated in the visit, including medical records on AEs, concomitant medications and any relevant data, records from the collection of blood samples, vital signs and other complementary exams, identification of the medication retrieved and dispensed, and patient questionnaires. The archiving of that information is essential to complete the CRFs and to prove that procedures were performed.

Regularly, I also verified if the patient's file had all the information required as per protocol and, if not, I gathered the information and archived it in the right section of the file.

2.2.1.2. The Study Procedures

Any clinical trial requires the completion of several procedures during its course, including measurement of vital signs, performing electrocardiograms (ECGs), dispensing the investigational product and processing, storage and shipping of biological samples. These procedures are defined in the study protocol and must be performed according to the instructions given in the study guidelines and/or manuals (e.g. laboratory manual and CRF completion guidelines).

2.2.1.2.1. The Interactive Response Technology (IRT)

The IRT is a software that is used in clinical trials to enroll and randomize subjects, manage clinical trial supplies (drug tracking, dispensing and reconciliation), discontinue the patient's treatment, set treatment completion and break blinding code (61). The most common types of IRT used in clinical trials are Interactive Voice Response Systems (IVRS) – automated telephone calls – and Interactive Web Response Systems (IWRS) – intuitive online systems (61).

During my curricular training in the CIC, I had the opportunity to learn how to work with the IVRS/IWRS technologies ClinPhone®, Almac®, Bracket®, Endpoint® and Oracle®. First, I was explained about the functioning of such systems and then I observed the CRCs of the unit using them. After receiving this training, I was able to use these technologies autonomously.

The use of any of these systems requires the confirmation of some information on the subject. Therefore, before using them, I identified that information and, after performing the assignments required, I received a confirmation, by email, and archived it in the patient's file.

2.2.1.2.2. Processing, Storage and Shipping of Biological Samples

In the CIC, for the majority of the clinical trials, it is function of the CRC the processing, storage and shipping of blood and urine samples.

The collection of blood samples is done using evacuated tube systems with interchangeable plastic tubes, all provided by the sponsor of each trial. The collection tubes, some with additives appropriate to a specific application, are differentiated by their color-coded stoppers and must be drawn in a specific order to avoid cross-contamination of additives. Before each visit, I had to prepare the corresponding laboratory kits, which included identifying the collection and interchangeable tubes and completing the requisition forms with the subject number and demographic data. If any of the samples needed to be shipped frozen, I also requested the central laboratory of the study to send dry ice to the CIC on the day of the visit.

During the collection of blood samples, I assisted the laboratory technician/study nurse, mainly by identifying the correct order of the collection tubes and agitating the samples to avoid hemolysis. After the collection of the samples, usually I needed to centrifuge them, according to the specifications given in the laboratory manual, and transfer the serum to the corresponding transfer tube(s). Some trials also required the preparation of blood smears. In these cases, I prepared the blood smears as described in the laboratory manual of the trial.

Regarding urine samples, some trials only required the samples to be sent if the urine analysis using a dipstick was positive. In these cases, I performed the analysis with the dipstick and sent the samples to the central laboratory if I found any abnormal result.

After processing the samples, I prepared them to be shipped according to the study instructions, gathered the waybills and called the courier to send the shipment to the central laboratory of the study.

2.2.1.2.3. Training on Technical Equipment for Clinical Trial Procedures

Besides processing, storage and shipping of biological samples, the CRCs of the CIC are also responsible for performing some trial procedures, such as measurement of vital signs and performing ECGs.

At the beginning of my training, I was explained on how to measure blood pressure, pulse, respiratory rate, temperature, weight and height. Thereafter, I was able to perform these tasks independently. Before performing any of these measurements, I had to consult the protocol of each trial to verify the specificities for the registration of each parameter.

Also, I received training on how to use the electrocardiograph. I learned how to introduce the subject's identification, place the electrodes, print the results and send the exams to the central team to obtain the clinical report. Although I have never performed an ECG autonomously, this training gave me the insight to certify the execution of this examination and intervene if the same was not being done properly.

2.2.2. Setting Up a Clinical Trial

Before any clinical trial can take place, several activities associated with identifying, qualifying, and activating an investigational site are carried out. The role of the CRC in these activities is crucial for the correct and successful implementation of the trial and for its proper conduction.

2.2.2.1. The Feasibility Process

Clinical trial feasibility is the process of evaluating the ability of an investigational site to conduct a particular clinical trial (62). Typically, the feasibility process includes two different approaches: a site feasibility questionnaire and a site qualification visit (62).

The site feasibility questionnaire is targeted towards the future PI of the study and assesses the investigator's experience, qualifications and interest in the research question, the availability of qualified staff to conduct the study, the suitability of the

patient population, the adequacy of site infrastructures, including the availability of any specialized diagnostic or therapeutic equipment, and the availability of time to conduct the trial (62).

The site qualification visit, also called pre-study visit, is conducted to verify the capability of the investigator and of the investigational site to conduct the study (62). During this visit, the monitor of the study discusses with the PI and the CRC the investigator responsibilities, the basic fundamentals of the study protocol (study objectives, protocol-required procedures and eligibility criteria) and how that relates to the feasibility of recruiting potential participants, and the AE reporting, source documentation, and record retention (62). Usually, it also includes a visit to the site facilities, including the pharmacy, to confirm that the site meets the space requirements for the study and the required equipment is available (62).

If the investigational site is eligible to conduct the clinical trial, the study team begins the preparation for the submission of the trial at the site. In the CIC, the CRC provides support to the study PI by preparing a letter to the president of the Ethics Committee requesting a review of the trial, obtaining the authorization from the Administrator of the Neurology Department and by reviewing the financial contracts.

Unfortunately, I have not had the opportunity to follow this phase of the process of setting up a clinical trial. However, despite the feasibility questionnaires and the site qualification visits vary greatly from sponsor to sponsor, the CRC of the CIC showed me some feasibility questionnaires and taught me how to complete them and explained me the general workflow of the visits, as well as the submission procedures in place in the CIC.

2.2.2.2. Investigator Meetings

The investigator meeting is a meeting held before the beginning of a clinical trial between the site staff and the sponsor study team to discuss the trial in general (therapeutic area, procedures and associated documents) and the investigational medicinal product (63). The investigator meeting is an opportunity for the research team to learn what the clinical trial will be like, to discuss potential issues and share strategies and best practices from previous studies (63).

During the period I was in the CIC, the CRCs of the sub-unit were able to attend some investigator meetings. As a trainee, I have not had the opportunity of attending any of these meetings. However, the CRCs explained me what was discussed and transmitted me the key knowledge that I was required to have to actively participate in the trials.

2.2.2.3. The Site Initiation Visit

The site initiation visit is when the research team receives adequate training from the sponsor on the study protocol for the proper conduction of the trial (64). During this visit, the whole study team and the sponsor discuss several aspects regarding the trial, including study design, objectives, eligibility criteria, procedures and access to suitable patient population, requirements for research sample processing and shipping, applicable regulations and GCP requirements, informed consent requirements, AE reporting, drug accountability, data forms completion, regulatory documents and study file organization (64). The site initiation visit is also an opportunity for team members to clarify their doubts concerning the trial (64).

The initiation visit is the last step before the study site is activated for enrollment by the sponsor (64). During my training in the CIC, I had the opportunity of participating in three site initiation visits. In these visits, I was able to gain an in-depth understanding on the trials and their procedures, and to know the study monitors. I also supported the monitors of the study in organizing the study cabinet, archiving documents in the ISF (correspondence that had already arrived at the site, delegation signature log, visit log and other essential documents) and verifying laboratory kits and other study equipment. After the visits, I also requested signatures whenever a member of the research team had not attended the visit.

2.2.3. Running a Clinical Trial

Once all the relevant approvals are in place, all documentation has been finalized, and the site has the appropriate and required training on the protocol, the trial can begin.

2.2.3.1. Preparing the Study Visits

Prior to each study visit, the research team must be prepared for all known and unknown tasks that may need to be completed as per protocol. A good preparation of the study visits is essential to avoid protocol deviations and to increase the quality of the generated data.

Most visits require a diversified clinical evaluation, with several clinical assessment procedures and involving several team members. The first step before a trial visit is to schedule all required procedures with all team members and the patient. When scheduling the evaluation procedures and the visit itself I remembered the team members about the tasks to be completed and informed patients on where the visit was going to take place and how long it would take, and any special instructions the patient

should follow prior to the visit. This was important to ensure protocol compliance. Once the visit was scheduled, a follow-up contact, usually in the form of a phone call, to the patient was performed to reinforce the requirements of the study and further explain important details of the upcoming visit.

Before preparing any trial visit, I had to review the protocol of the trial, with special attention to the core assessments of the concerned visit, as well as the patient's file, in order to be able to resolve pending issues and/or those that could arise during the visit. After that, I prepared the visit, which usually included completion of required physician orders, such as the medication prescription form, preparation and provision of laboratory kits to the appropriate clinical team to draw the samples, preparation of patient questionnaires and of worksheets and checklists with all visit procedures indicated per protocol to aid investigators conducting the visit and to ascertain that required data was collected.

When preparing a visit, I also had to consider the possibility of the patient deciding to withdraw from the study or to be withdrawn by the study investigator due to AEs or any other clinical relevant reason. Therefore, before each visit, I had to review the end-of-study visit procedures and to know where the visit items were to be readily available, if these situations happen.

2.2.3.2. The Study Visits

Usually, all clinical trials have a screening visit, in which the study investigator determines if the patient is eligible to participate in the trial; a randomization visit, where the patient is assigned to the study treatment(s); the treatment visits, aimed at assessing the effect of the study treatment(s); an end-of-treatment visit, to conclude the participation of the patient in the trial; and a follow-up visit, carried out to monitor the safety of the patient. The course of each visit is determined by the study protocol.

2.2.3.2.1. The Screening Visit

Before any study-specific procedures or evaluations can take place, the patient must sign and date the ICF, after a comprehensive discussion with the investigator of the study. During this process, I supported the investigator by clarifying any questions regarding the trial that had arisen during the discussion and by explaining the logistic aspects of the trial to the patient, such as where were the different visits/assessments, how was transportation handled and how were expenses reimbursed. I also made a copy of the signed ICF to deliver to the patient.

Once the consent form had been signed by all applicable parties, I registered the patient in the IVRS/IWRS system to obtain the patient's screening number, which

identified him/her in the study. After registering the patient, I performed the study procedures that could be done at the same day of the visit. These usually included measurement of vital signs, performing an ECG, processing of laboratory samples and delivery of patient questionnaires. Besides performing these procedures, I also scheduled the ones that could not be done at the visit (e.g. ophthalmology exam, pulmonary function test, dermatology assessment), always considering the window timeline required by the protocol. At the end of the screening visit, I gave the patient an identification card identifying him/her as a participant in the clinical trial and containing trial site contact information (including direct telephone numbers) to be used whenever necessary.

In this visit, it is important to collect the medical history of the patient in a detailed and thorough way, as well as other relevant clinical data, such as demographics, as established in the study protocol. To ensure these data were collected, before each visit, I prepared checklists and worksheets identifying the information to be recorded in the medical file of the patient.

If the patient did not meet one or more criteria required for participation in the trial, after signing the ICF, the patient was considered a screening failure and I reported it in the IVRS/IWRS system.

During my training, I performed five screening visits and supported the other CRC's performing 13 visits. Of these 18 screenings, four were considered screening failure.

2.2.3.2.2. The Randomization Visit

The randomization visit corresponds to the treatment initiation. After the investigator of the study confirmed that the patient met all inclusion criteria, I performed his/her randomization to one of the study treatment arms using the study IVRS/IWRS system. Once the investigational product has been dispensed by the pharmacy, I gave it to the patient and explained him/her on how to take/administer it. Usually, the first dose of the investigational product was taken/administered in the CIC to monitor the safety of the patient.

At this visit, and when applicable, I also delivered to the trial patient a study medication diary to record information about medication use. Therefore, I had to instruct the patient to record the study drug intake, according to the instructions given in the study protocol/study medication diary manual.

In addition to the randomization of the patient, I performed and/or helped to perform the other specific procedures of the visit (measurement of vital signs, performing ECG, processing, storage and shipping of laboratory samples and delivery

of patient questionnaires) and scheduled the ones to be performed outside the CIC, as specified in the study protocol.

In the scope of my training, I had the opportunity of performing five randomization visits and of providing support to the CRCs in 12 other visits.

2.2.3.2.3. The Treatment Visits

The course of each treatment visit is established by the study protocol and is related to the purpose of the trial. Despite the differences between treatment visits of the same trial and between visits of different trials, there are a set of activities that are responsibility of the CRC and are similar for all treatment visits. The main differences are regarding scheduling of specific assessment procedures (e.g. neuropsychological, ophthalmology, pulmonary function and dermatology).

Therefore, in any treatment visit, I remembered the study investigator on the information that should be recorded in the patient's medical file, measured vital signs, assisted in performing the ECG and delivered the patient questionnaires to the patient. In this later step, I instructed the patient on how to complete the questionnaires and, before the end of the visit, I checked if they were correctly answered to avoid missing data. If the visit required the collection of biological samples, I processed the samples, stored the ones to be left in the CIC as backup and sent the others to be analyzed in the central laboratory.

Also, I registered the visit in the IVRS/IWRS system and ordered a medication resupply to dispense new medication to the patient. Before making the dispensing, I received the returned medication and made the medication reconciliation to assess compliance. After that, I delivered it to the patient and reinforced the indications on how to take it and reminded him/her to bring the unused medication and the empty packaging on the next visit. Regarding the study medication diary, I collected it and delivered a new one.

During the treatment period, it is frequent that ICFs are reviewed. Every time a new addendum was made to the ICF, I reminded the investigator to explain to the patient the change(s) and to give him/her the new version to be signed and dated. Then, I made a copy of the new signed ICF and delivered it to the patient.

In my training, I performed treatment visits for all clinical trials in which I was engaged, except for one (Table 2).

2.2.3.2.4. The End-of-Treatment and the Follow-up Visits

An end-of-treatment visit is scheduled when the patient has completed the treatment period, as defined by the protocol of the study. After the end-of-treatment

visit, usually one month later, a follow-up visit is performed. The follow-up visit is conducted mainly to collect information on AEs.

Sometimes, it happens the patient discontinues the trial investigational product prematurely. In this case, the visit end-of-treatment – premature discontinuation is scheduled shortly after the patient has discontinued the trial investigational product. Patient discontinuation can be due to progression of disease, unacceptable toxicity, AEs, non-compliance with the study protocol, investigator decision, pregnancy or withdrawal of consent.

During the six months I was in the CIC, I had the opportunity of performing one end-of-treatment and two follow-up visits. In the end-of-treatment visit, besides performing and scheduling the usual procedures, I made the discontinuation of the patient in the IVRS/IWRS system, retrieved all the investigational products that the patient had, collected the study medication diary and performed the final drug accountability. In the follow-up visit, I performed the procedures specified in the protocol that were responsibility of the CRC (measurement of vital signs and processing, storage and shipping of laboratory samples).

2.2.3.2.5. After the Visit

After each visit, I gathered all the information collected during the visit as well as the information that was generated. This information was then reviewed to ensure that all necessary data was collected and to check its consistency and transcribed and/or uploaded into the study CRF.

CRFs are data collection tools, provided by the clinical trial sponsor, that are designed to record all of the protocol-required information to be reported to the sponsor on each trial participant (65). The CRF completion allows the capture, review, management, storage, analysis, and report of data, in a systematic basis (65). There are two types of CRFs used in clinical research – paper CRFs and electronic CRFs (eCRFs) (65). During my training, I had the possibility of working with both types of CRFs. However, I preferred working with eCRFs as they have built-in edit checks tagged to each data field, as well as to the CRF as a whole.

The majority of the clinical trials being conducted in the CIC during my training used eCRFs. Before using any of these systems, I received training from the CRCs of the sub-unit on how to access the CRF, make data entry, validate and correct data, and answer queries, according to the eCRF completion guidelines. The most commonly used systems in my training were Inform™, Think Trial™, Viedoc™, QCAT™, Medidata Rave™, BioClinica Express™ and RDC Onsite™. In some of them,

I had to transcribe data present in the source documents (e.g. RDC Onsite ™ and Inform™) and in others I had to directly upload data (e.g. QCAT™).

After transcribing/uploading the data on the CRF, I archived all source documents in the patient's file and sent the ECG, if performed, from the electrocardiograph to the central reading laboratory, by phone line. Also, if the investigator had reported an AE or a Serious Adverse Event (SAE), I verified the completeness of the report to be sent to the sponsor, sent it and transcribed it into the CRF, and made the follow-up of the event.

2.2.3.2.6. Closing Out the Clinical Trial and Archiving Essential Documents

A close-out visit occurs once the patients are no longer being dosed and all the data have been collected, including complete follow-up of AEs/SAEs and resolution of all outstanding queries (66). At this time, the study database is locked and ready for statistical analysis (66).

The purpose of this visit is to assure that the study is complete, all study supplies and investigational agents are returned to the sponsor, the study documentation is in place and data is accurate, and to discuss the requirements for retention of study materials (66). Therefore, it is important that the investigator and the other study team prepare for the closeout visit.

During my training, I was able to collaborate in the preparation of one close-out visit. This involved reviewing the study files for completeness and accuracy, consolidating all records into one set of study files, completing and having the investigator reviewing and signing all CRFs, assuring that the subjects' medical records and clinic charts were available for the monitor to verify data and address queries, having all subjects' signed ICFs available for review and storage with the study records, resolving any outstanding discrepancies identified on previous periodic site visits, amongst others. In this visit, the CRC should make sure that the sponsor returns all study supplies and medications, shipment receipts are complete and accurate and copies are placed in the regulatory binder.

After the close-out visit, all essential documents should be archived. Essential documents are "those documents that individually and collectively permit the evaluation of the conduct of the trial and the quality of the data produced and show whether the trial is, or has been, conducted in accordance with the applicable regulatory requirements" (25). These documents include the ISF and participant CRFs and source documents (25). The study documentation must be retained for at least 5 years after the conclusion of the trial, as defined in the Decree-Law 102/2007 of April 2nd (34), or

for 15 years, as defined in the ICH GCP E6 guidance (25), and, during that period, readily available to the regulatory authorities on request (25,34).

2.2.4. Other Activities of a Clinical Research Coordinator

Besides preparing and conducting study visits, there are several other activities that must be performed in a clinical research center to ensure the proper conduction of clinical trials.

During my training in the CIC, I supported the CRCs of the sub-unit clarifying outstanding issues and new updates of the studies together with the study monitors, replying to e-mails from the investigators, monitors and other parties involved in the studies, and delivering to the investigators reports of suspected unexpected serious adverse reactions and other study documentation to be signed by them. Also, I updated the ISF archiving correspondence, newsletters and other study information, and filling the patient identification log, the screening log and the sample logs on an ongoing basis.

After data entry, queries may be generated. Queries are any errors, omissions, or items requiring clarification or changes to the CRF that are detected during the data entry and verification process, by computer edits or during data analysis (67). The prompt resolution of queries is important so that the analysis of the data is not compromised. Therefore, regularly I checked the CRFs of the trials to verify if there were any pending queries and tried to resolve them. Sometimes, the complexity of the queries required me to contact the study monitors. If the queries had to be resolved with urgency, usually, the study monitor sent an email identifying the open queries and with some guidance to answer them.

Regularly, I also had to check the material stock of each clinical trial in order to ensure that the material required for each visit was available when needed. Therefore, I checked the laboratory kits that were running out or that were expiring soon, ECG electrodes, patient's diaries and other materials specific to each clinical trial, in order to ask the sponsor for replacements.

Furthermore, once a month, I downloaded the freezer temperature logs and, when there was a large number of samples in the freezer, I made a list identifying the samples that were stored to send the samples that could be sent and left only those which had to stay as backup.

In the CIC, every Friday a calendar with the following week's visits, indicating the protocol number, the number of patients and the scheduled times, was sent to the pharmacy, the study nurses and the psychologists to ensure the proper conduction of

the trial visits. During my curricular training, I was responsible for preparing the calendar and sending it to the appropriate team members. Besides that, every Friday I also identified the next week visits that required samples to be sent frozen and asked the central laboratory to send dry ice for the day of the visit.

2.2.5. Periodic Monitoring Visits

The most significant interactions between the CRC and the study sponsor occur during site monitoring visits. Throughout the course of a clinical trial, several periodic monitoring visits are carried out to assess the progress of clinical trials, verify adherence to the study protocol, check if the reported data is complete and consistent with the source documents, and ensure patient safety and compliance with ethical and regulatory requirements (66).

During my training in the CIC I had the opportunity of actively participating in periodic monitoring visits of two clinical trials. Before each visit, I had to complete all necessary CRFs, confirm that SAE forms have been submitted and were available for review, obtain medical records for CRFs to be reviewed, organize study file documents, confirm that signed ICFs for all enrolled participants were available and review if all pending issues from the last monitoring visits were resolved. Also, I gathered all doubts regarding the trial (e.g. completion of CRFs, performance of specific procedures) to clarify with the monitors of the studies. During the visits, I assisted the monitors understanding the reported data and, after the visit, I discussed with them the findings from the monitoring and started answering them.

2.2.6. The Most Involving Clinical Trial – The Expand Trial

The Expand trial, a multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of siponimod (BAF312) in patients with secondary progressive multiple sclerosis, is a phase III clinical trial sponsored by Novartis. The study's primary objective is to demonstrate the efficacy of siponimod relatively to placebo in delaying the time to confirmed disability progression as measured by the Expanded Disability Status Scale (68). The secondary outcome measures include the efficacy of siponimod relatively to placebo on mobility and leg function and in reducing the increase in CNS lesion volume, impact of multiple sclerosis on the individual's walking ability and number of AEs, amongst others (68).

Although I have participated in almost all trials ongoing in the CIC at the time of my curricular training, the Expand trial was the study in which I was more active and autonomous. When I started collaborating in this trial, the patients were already in the

treatment phase. Therefore, I received training on this clinical trial (procedures and assessments, requirements for research sample processing and shipping, data forms completion and study file organization) from the previous CRC responsible for the trial.

The Expand trial was a relatively complex trial due to the number of procedures/assessments required by the protocol and the number of team members involved. Besides preparing and conducting trial visits, providing backup to the investigator, completing the eCRF and answering queries, receiving monitoring visits and managing documentation related to the trial, I had to schedule all procedures/assessments, always considering the window timeline established by the protocol, and handle transportation requests.

Since this trial had a lot of procedures/assessments and a specific order to carry them out, a thorough organization was almost mandatory. Therefore, I developed checklists and worksheets with all visit procedures indicated per protocol for each visit and identifying the order to be followed. This was important not only to ensure protocol compliance but also to plan the visits to be as time efficient as possible, since long visits were very tiresome for the subjects.

2.2.7. Coordination of Observational Studies

My activities as a CRC were developed in the context of clinical trials. However, during the time I was in the CIC, I had the opportunity of actively collaborating in the coordination of observational studies. An observational study is a study where the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice (31).

During my training, I collaborated in the introduction of data into the eCRF of an observational study on idiopathic cervical dystonia. However, the study in which I participated more thoroughly was the REGISTRY study. In this last study, I helped the CRC scheduling study visits according to the availability of the study investigators, preparing and conducting study visits, providing support to study patients completing self-report questionnaires and preparing and shipping biological samples to the central laboratory.

2.2.8. Site Monitoring Visit

Within the scope of the REGISTRY study, I was able to accompany a site monitoring visit. The REGISTRY is a project of the European Huntington's Disease Network, a Europe-wide network of professionals and people affected by Huntington's disease (59). As a part of this network, the HSM has an active participation in this study. The HSM is the Portuguese language area coordinator of REGISTRY, being

responsible for coordinating and monitoring the study in all Portuguese centers participating in it.

One of the CRCs of the CIC also accumulates functions as monitor of this study. The monitoring of the REGISTRY is divided into two components, on-site monitoring and remote monitoring. The remote monitoring is performed to data that does not have source documents and, therefore, is directly introduced in the eCRF, and is based on the verification of the consistency of the data entered. On-site monitoring, on the other hand, is performed whenever data is transcribed into the eCRF.

The site monitoring visit I was able to accompany was performed in a local hospital in Lisbon. During this visit I helped the monitor of the study verifying if previous queries where answered properly and if the protocol was being followed and reviewing the study documentation to identify data entry errors and missing data in the patients records or eCRFs. Whenever data entered was not in accordance with source documents or data was incomplete, I helped the monitor of the study generating queries to be reviewed by the investigational team.

3. Discussion

Clinical trials are a key part of the development of new health interventions as they allow researchers to demonstrate the efficacy and safety of a new medicine or treatment in humans, which is a prerequisite to get regulatory approval (69).

Considering the importance of clinical trials, for the second year of my Master's degree in Pharmaceutical Biomedicine, I decided to enroll in a curricular training in clinical trials coordination. The characteristics of the UFC, host institution of this training, allowed me to participate in several activities relating to different stages of the development of new health interventions, which made this experience a very enriching one.

The CIC is a very well organized research unit with several years of experience and with dedicated and qualified staff in the coordination of clinical studies, who were always eager to share their knowledge and experience in clinical research and to help me deepen my knowledge and became a better professional.

When I started my training in the CIC, the research team was experiencing a reformulation since one of the CRCs left the team. Therefore, right from the start of the training, I was asked to assume a very active role in the coordination activities, which was quite complicated to me as I had no previous experience. At the beginning it was difficult to understand how to handle with study documentation and the order and timing of the different study procedures, to identify the research team of each study and to apply some study procedures. However, I always felt supported by the other CRCs of the CIC who helped me overcoming these difficulties and clarified my doubts. First, I was mainly responsible for archiving the study documentation and processing and shipping biologic samples. As the training evolved, I was able to start performing activities that required more responsibility, such as managing patient visits by myself, communicating directly with the monitors of the trials to resolve outstanding issues and making reimbursements of patients' expenses.

During my curricular training in the CIC, there were 22 clinical trials and 10 observational studies ongoing. Although I have not participated in all of them, I was able to work in different studies. This was a unique opportunity to contact with protocols with different levels of complexity, study designs and procedures, from distinct sponsors and in several pathologies. I learned a lot from reading the study protocols and from applying their procedures and I became more proficient in understanding this type of documents. This training experience was even more enriching as I was able to participate in the coordination of trials from different phases. In fact, the only trial phase

I was not able to work in was phase I. Also, this was an opportunity to consolidate my background knowledge on the pathologies I worked, alongside the current available treatments.

During my training in the CIC I had the chance of working with different types of medications, biologics and chemically derived drugs. This was an important aspect of my training as I was able to see and understand the different requirements for handling these types of medications and the procedures for the preparation of patients before the administration and for the administration of the drug. Also, I noticed the different types of AEs that may occur with each type of medication and the specificities of the data to be reported.

A CRC is someone who is constantly communicating with different stakeholders in clinical research, from the investigators and remaining site staff, to the study monitors and other representatives of the study sponsor, and who ensures the completeness, consistency and integrity of the data reported, the good progression/flow of the trial, and protocol compliance. Performing these activities was very important for me to improve my communication and organization skills and to become more attentive to detail, focused and more stringent in terms of quality of work. Also, this training allowed me to improve my ability to work in teams. Every day we had appointments of more than one trial, with several procedures and a lot of information to manage. Therefore, we had to work as a team to ensure everything was done right.

Coordinating clinical trials in the CIC was a constant challenge and learning experience. The high number of clinical trials and observational studies ongoing in the CIC required me to perform several different procedures, which I think was a great opportunity to complement the knowledge acquired in each study. Also, the unpredictability of dealing directly with patients was very important for my professional growth. During the six months I was in the CIC, there were many the situations where every procedures were scheduled and all things were prepared and the patient did not show up or just canceled the visit the day before because he/she did not want to come or was not feeling well, making it difficult to re-scheduled everything within the therapeutic window of the visit. However, with the experience of the CRCs of the CIC, I learned how to proceed in these situations and, in the end of my training, I was quite autonomous to resolve these problems.

The training in clinical trials coordination was also very rewarding for me as I could see and apply the knowledge acquired previously in the Bachelor's Degree and in the first year of my Master's Degree and complement the concepts learned. It was very motivating for me to see the applicability of all the subjects I learned during the last four years in a real world context and to look at things from a new perspective, the

on-the-job perspective. This complementarity makes me feel that I am even more prepared to become a professional of clinical research.

During the training in the CIC, I was able to closely experience the main hindrances of running clinical trials in neurology. As mentioned above, clinical trials in neurology have very restrictive inclusion criteria and exhaustive evaluation processes/tools and lack of objective effect measures (16). As the HSM is a central hospital, the investigators from the CIC see many patients every day, including *de novo*; still, for some clinical trials, it was difficult to include patients and reach the agreed number of participants. Even after a pre-selection of patients using databases with clinical data, it was difficult to identify those that met the restrictive inclusion criteria. Also, for almost all trials in which I worked, patients had to stay in the CIC for several hours or come to the CIC and other institutions involved in the trial several times, due to the exhaustive evaluation processes and tools. For some of the trials, patients had to stay in the CIC during the whole morning or even the whole day. Another reality I could experience was the lack of objective measures of the effect of drugs. The vast majority of the clinical trials in CIC used only evaluations that included level of cognitive or physical function, which can be subject to variation in reporting by patients or investigators. This was quite interesting for me as I saw in the field what I learned in theory, by reading papers and other publications.

The main difficulty I felt in this training was to manage clinical trials in which I was not involved from the beginning. It was hard for me to realize the dynamics of the study visits, what procedures should be done first, in what substudies the patients were participating, and answer queries and solve other issues regarding the study before I started working on it. Another difficulty I felt was to conciliate all the procedures that had to be done for the study visits, within the given therapeutic window, due to the different availability of the involved parties. Contrary to what I first thought that would be my main difficulty, the contact with the patients was pretty easy. I always felt comfortable talking with them and performing the study procedures.

Besides the achievements I made, I think there was an important gap in my training. In the CIC, the CRC is responsible for the coordination of the submission process of the trial documentation to the Ethics Committee and the Administration Board of the HSM and the Administrator of the Neurology Department. Although I was explained about this process, I was not able to participate in it, which makes me feel that I am not prepared to do this task by myself.

With this training I realized that the conduction of a clinical trial is a very demanding task that requires strict adherence to the study protocol and a thorough logistics preparation and that being a CRC is much more than ensuring protocol

compliance and quality of data. The CRC plays a pivotal role in clinical trials by managing the anxieties and expectations of patients with the clinical research they are enrolled in, assisting study monitors and facilitating the communication between investigators, patients, monitors and other sponsor representatives.

After the 6 months of training in clinical trials coordination, I strongly believe that I met all the objectives I have set for this training. From preparing and conducting study visits, measuring vital signs and processing and shipping of biological samples, to completing CRFs, answering queries, using IVRS/IWRS systems, assessing compliance with the study medication, archiving study documentation and monitoring data quality, I learned to perform all these activities. After this training, I believe that I am well prepared to become a CRC. Also, I believe that starting my career in clinical trials coordination was a very good basis to perform other functions in clinical research.

The opportunity of experiencing the activity of monitoring of clinical trials was a good complement to my training. In the site monitoring visit that I participated in, I learned different methodologies of work, including different ways of organizing a research site and the study documentation, learned how to do source data verification and practiced data quality control. The possibility of seeing how other research teams work was very enriching as I could find ways to improve my working methods to be more efficient and do things better.

Despite the importance of coordination of clinical trials, I cannot devalue the contribution of all the other activities carried out during this 10 month training for my personal and professional growth. From drawing-up a quality control plan, receiving, validating and processing of spontaneous reports of ADRs and collaborating in the writing of scientific papers, to the courses I was able to attend and all the other activities I have done, I consider that I have gained a very good background knowledge to start my professional career.

The data management activities I was engaged in were very important as I had no previous theoretical and/or practical knowledge on this matter. During my academic education this was a subject that was not explored in detail and, therefore, I had little knowledge on the matter. This training provided me the opportunity of learning what is data management, how is it done and why is it important. The most interesting thing in this training was to see data quality control applied within the scope of data management activities. Also, it was very important for me to understand the relevance of collecting complete data in clinical studies, as missing data may lead to the exclusion of a research participant from data analysis, compromising the assessment of the effect of the intervention under study. I believe that accomplishing the training in

data management before starting the activities of clinical trials coordination made me more demanding in terms of data collection and reporting.

My training in the URFLVT was also a very interesting experience as I could realize the importance of pharmacovigilance. All medicinal products are subject to several clinical trials to assess their quality, efficacy and safety before being authorized (70). However, clinical trials have several methodological limitations that do not allow the obtainment of a comprehensive knowledge of a drug safety profile (70). In fact, the experimental environment is significantly different from that in which the drug will be used in clinical practice (70). Therefore, it is essential to have oriented structures for drug safety monitoring once drugs are placed on the market and start being used on a large scale by patient groups in which they have not been investigated and in very different conditions from those in which they were developed.

Although my training in the URFLVT was short, it was enough for me to realize the background knowledge that performing pharmacovigilance activities requires. Being engaged in pharmacovigilance activities requires a deep understanding and knowledge on the legislation in force, medicines available in the market (indication, dosage strength, formulations, …) and diseases. In my training, I learned how to validate reports according to pre-specified criteria, how to introduce data in *Portal RAM*, how to send data to the SVIG and how to make requests for additional information.

One of my main difficulties during this training in pharmacovigilance was to classify ADRs as described/non-described, according to the information of the summary of the product characteristics, since it was necessary an adequate knowledge to verify whether a reported term was equivalent to the ADR or not. Therefore, I always had to confirm with the two pharmaceuticals of the unit if my classification was correct. Also, I had difficulties coding ADRs using the MedDRA as I had to use the term that was closest to that reported and that term was not always available in the dictionary. In turn, as the training progressed, I learned from my mistakes and became more proficient coding ADRs. Due to my limited knowledge, mainly regarding the specificities of medicines (dosage strength and formulations), I also felt difficulties identifying the questions to address to the reporters to request for additional information. However, with the experience gained during the training, I am now more capable to do those requests.

Despite the mentioned difficulties, I consider that this training in the URFLVT was very important. I learned, as a professional and as a citizen, the importance of doing a good report of a suspected ADR, mainly the importance of providing the largest possible amount of information about the ADR, the suspected drug and any

concomitant medication and diseases, to better assess the probability of the drug causing the ADR. Also, learning to code medical information with the MedDRA was an added value for my training, as working with the MedDRA is almost mandatory in the pharmaceutical field and I have never had that chance before.

As for medical writing, this was a great opportunity for me to improve my writing skills. I had the opportunity of collaborating in several different research projects, from applying their methodologies to writing some parts of their papers. I learned how to write in an objective, clear and scientifically correct way and I could see the evolution of my writing abilities over the projects in which I participated in. The medical writing activities I engaged in also gave me the unique opportunity of publishing, as a co-author, in a peer reviewed journal.

Besides the activities I was able to carry out during this 10 month period, I also have to mention the great opportunity that was being able to attend the meetings of the research teams of the CIC and UFC and all the courses facilitated by them. The discussion of research papers, mainly their methodologies and limitations, and of research projects of some members of the group was a unique opportunity for me to deepen my knowledge on these subjects. Also, the discussion of recent papers allowed me to be aware of what was being done in clinical research in neurology, what was being discovered and what was being made to increase the quality of life of people suffering from neurological diseases. The courses I attended were an opportunity for me to deepen and refine the knowledge previously acquired in the Bachelor's and Master's Degrees.

Considering the above, I believe that the characteristics of the host institution, the UFC, were the main factor that most influenced the success of my training. Its well-defined structure, as well as the professionals that constitute the research group, who have a deepen knowledge in clinical research and a strong desire to teach and share their knowledge, and the working principles and values of the group, mainly the cooperation and teamwork, were fundamental for me to reach my objectives and successfully finish my training.

4. Conclusion

My curricular training in the UFC was a very rewarding and enriching experience. I had the opportunity of participating in several research projects, from coordinating clinical trials to performing data management, pharmacovigilance and medical writing activities, and working with different groups, with very different backgrounds and experiences.

This training in the UFC allowed me to refine and complement the knowledge previously acquired in the Bachelor's and in the Master's Degrees, mainly on GCP, clinical drug development and drug lifecycle, medicines regulation and ethics in clinical research. It was also an opportunity for me to develop hard and soft skills that will help me to become a better professional. I improved my organizational and communication skills and ability to focus and learned to better work in teams and plan things. As my training evolved, I engaged in more activities and responsibilities, which helped me to become more autonomous and more confident with my work.

After this training, I can say that I meet all my primary objectives. The possibility of participating in the coordination of clinical trials of different phases and in several neurological diseases allowed me to learn and practice a broad range of activities and to increase my knowledge regarding clinical research. Working in a team such as the CIC gave me a real insight about the environment of clinical research and was an opportunity to understand the functioning of an organized and recognized clinical research center.

Regarding the secondary objectives, I learned how to do clinical trial monitoring, become capable of receiving, validating and processing spontaneous reports of ADRs, developed skills in clinical data management and improved my medical writing skills. With these activities, I got a perspective on the process of the clinical development of new medical products, besides the conduction of clinical trials. Also, I could understand how these different fields relate to each other.

Overall, I would say that my training has become more than I have ever expected. Every day was a constant learning experience and a challenge that made me grow up professionally and personally. I believe that with this training I am well prepared to start my professional career and to perform different functions in clinical research.

5. References

1. Instituto Medicina Molecular. 2013 Activity Report [Internet]. 2014. p. 5. [cited 2015 Jul 1]. Available from: https://imm.medicina.ulisboa.pt/files/2914/3213/6597/IMM_Report_2013.pdf.
2. Ferreira J. Proposal for the creation of a Clinical Pharmacology Unit at Instituto de Medicina Molecular. 2013. p. 22–7. Internal document.
3. Ferreira, Joaquim Lab [Internet]. Instituto Medicina Molecular - Universidade de Lisboa. 2015 [cited 2015 Jul 1]. Available from: https://imm.medicina.ulisboa.pt/pt/investigacao/laboratorios/ferreira-lab/.
4. Instituto Medicina Molecular. Scientific Report 2014 [Internet]. 2015. p. 180-201. [cited 2015 Jul 2]. Available from: https://imm.medicina.ulisboa.pt/files/5914/3948/2633/IMM_Scientific_Report_2014.pdf.
5. Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Junqueira Polónia J, Costa-Pereira A. O Sistema Português de Farmacovigilância. Acta Med Port [Internet]. 2012;25(4):241–9. [cited 2015 Jul 2]. Available from: http://www.actamedicaportuguesa.com/revista/index.php/amp/article/viewFile/67/55.
6. Rosa MM, Anes AM, Espada N. Manual da Qualidade. Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo; 2014. p. 6–10.
7. About Research & Development [Internet]. International Federation of Pharmaceutical Manufacturers & Associations. 2015 [cited 2015 Jan 18]. Available from: http://www.ifpma.org/innovation/rd/about-research-development.html.
8. Pharmaceutical Research and Manufacturers of America. 2015 Profile Biopharmaceutical Research Industry [Internet]. 2015. p. 33–46. [cited 2015 May 9]. Available from: http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf.
9. Pharmaceutical Research and Manufacturers of America. The Biopharmaceutical Pipeline: Evolving Science, Hope for Patients [Internet]. 2013. p. 1. [cited 2015 Jan 18]. Available from: http://www.phrma.org/sites/default/files/pdf/phrmapipelinereportfinal11713.pdf.
10. Pharmaceutical Research and Manufacturers of America. Drug Discovery and Development - Understanding the R&D Process [Internet]. 2007. p. 1–16. [cited 2015 Jan 19]. Available from: http://cmidd.northwestern.edu/sites/all/files/Drug_RD_Brochure.pdf.
11. Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther [Internet]. 2010;87(3):356–61. [cited 2015 Jan 22]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953249/.
12. Tufts Center for the Study of Drug Development. Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion [Internet]. 2014 [cited 2015 Jun 12]. Available from: http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.
13. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand

challenge. Nat Rev Drug Discov [Internet]. 2010;9(3):203–14. [cited 2015 Jan 22]. Available from: http://www.nature.com/nrd/journal/v9/n3/full/nrd3078.html.

14. Pharmaceuticals and Life Sciences. Pharma 2020: Virtual R&D - Which Path Will You Take? [Internet]. 2007. p. 6–14. [cited 2015 Jan 24]. Available from: http://www.vph-institute.org/upload/pwc-pharma2020-virtualrd-final_519245021a53a.pdf.

15. Clinipace Worlwide. Challenges and Opportunities in Developing Neurologic Therapies [Internet]. 2012. p. 1–8. [cited 2015 Jan 24]. Available from: http://www.clinipace.com/stuff/contentmgr/files/0/e2565a8ecfc96962d3f3293d583ae0b2/download/challengesinneurodrugdevelopment.pdf.

16. Skripka-Serry J. The great neuro-pipeline “brain drain” (and why Big Pharma hasn’t given up on CNS disorders). Drug Discovery World [Internet]. 2013;9–16. [cited 2015 Jan 25]. Available from: http://www.ddw-online.com/therapeutics/p216813-the-great-neuro-pipeline-brain-drain-(and-why-big-pharma-hasn-t-given-up-on-cns-disorders)-fall-13.html.

17. Pharmaceutical Research and Manufacturers of America. Medicines in Development for Neurological Disorders [Internet]. 2015. p. 1-4. [cited 2015 May 22]. Available from: http://phrma.org/sites/default/files/pdf/meddevelopment_neurologicaldisorders.pdf.

18. UCB. UCB Full-year Report 2010: a year of strong delivery [Internet]. 2015 [cited 2015 Oct 1]. Available from: http://www.ucb.com/presscenter/News//article/UCB-Full-year-Report-2010-a-year-of-strong-delivery.

19. The Innovative Medicines Initiative [Internet]. Innovative Medicines Initiative. 2010 [cited 2015 Jan 26]. Available from: http://www.imi.europa.eu/content/home.

20. Innovative Medicines Initiative. The Innovative Medicines Initiative (IMI) Research Agenda - Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society [Internet]. 2008. p. 49–53. [cited 2015 Jan 26]. Available from: http://www.imi.europa.eu/sites/default/files/uploads/documents/imi-gb-006v2-15022008-research-agenda_en.pdf.

21. Innovative Medicines Initiative. The right prevention and treatment for the right patient at the right time - Strategic Research Agenda for Innovative Medicines Initiative 2 [Internet]. 2014. p. 40–2. [cited 2015 Jan 26]. Available from: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf.

22. EU Joint Programme - Neurodegenerative Disease Research [Internet]. JPND research. 2014 [cited 2015 Feb 1]. Available from: http://www.neurodegenerationresearch.eu/.

23. Network of Centres of Excellence in Neurodegeneration Research (COEN) [Internet]. JPND research. 2015 [cited 2015 Jan 28]. Available from: http://www.neurodegenerationresearch.eu/initiatives/network-of-centres-of-excellence/.

24. National Institutes of Health. NIH Clinical Research Trials and You [Internet]. 2015 [cited 2015 Oct 1]. Available from: http://www.nih.gov/health/clinicaltrials/basics.htm.

25. ICH Harmonised Tripartite Guideline - Guideline for Good Clinical Practice

E6(R1) [Internet]. 1996. p. 1–41. [cited 2015 Feb 5]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

26. Clinical Trials [Internet]. World Health Organization. 2015 [cited 2015 Jan 26]. Available from: http://www.who.int/topics/clinical_trials/en/.

27. ICH Harmonised Tripartite Guideline - General Considerations for Clinical Trials E8 [Internet]. 1997. p. 5–8. [cited 2015 Feb 6]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf.

28. Evens RP. Chapter 5: Types of clinical studies. In: Evens RP, editor. Drug and Biological Development - From Molecule to Product and Beyond. Boston, MA: Springer US; 2007. p. 107–22.

29. Fefer E. Chapter 6: Pharmaceutical legislation and regulation. Managing Access to Medicines and Health Technologies [Internet]. VA: Management Sciences for Health; 2012. p. 100–20.

30. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. World Medical Association. 2015 [cited 2015 Jan 19]. Available from: http://www.wma.net/en/30publications/10policies/b3/.

31. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [Internet]. Official Journal of the European Communities; 2001 p. 34–44. [cited 2015 Jan 19]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF.

32. Lei n.º 21/2014, de 16 de abril [Internet]. Portugal: Diário da República, 1.ª Série - N.º 75 - 16 de Abril de 2014; 2014 p. 2450–65. [cited 2015 Jan 19]. Available from: http://app.parlamento.pt/webutils/docs/doc.pdf?path=6148523063446f764c3246795a5868774d546f334e7a67774c336470626e526c654852766331396863484a76646d466b62334d764d6a41784e43394d587a4978587a49774d5451756347526d&fich=L_21_2014.pdf&Inline=true.

33. Commission Directive 2005/28/EC of 8 April 2005 [Internet]. Official Journal of the European Union 2005 p. 13–9. [cited 2015 Jan 19]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf.

34. Decreto-Lei n.º 102/2007, de 2 de Abril [Internet]. Portugal: Diário da República, 1.ª Série - N.º 65 - 2 de Abril de 2007; 2007 p. 2078–84. [cited 2015 Jan 19]. Available from: http://www.sg.min-saude.pt/NR/rdonlyres/B9EBB192-952E-4C97-94FD-6B54A9F75A58/22166/20782084.pdf.

35. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 [Internet]. Official Journal of the European Communities 1995 p. 31–50. [cited 2015 Jan 19]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31995L0046&from=PT.

36. Lei n.o 67/98 de 26 de Outubro [Internet]. Portugal: Diário da República — I Série A - Nº 247 - 26-10-1998; 1998 p. 5536–46. [cited 2015 Jan 19]. Available from: http://www.dgpj.mj.pt/sections/estatisticas-da-justica/legislacao/lei-n-67-98-de-26-de/downloadFile/file/L_67_1998.pdf?nocache=1253185026.86.

37. Deliberação Nº 227 /2007 [Internet]. 2007. p. 1-15. [cited 2015 Jan 19]. Available from: http://www.cnpd.pt/bin/orientacoes/DEL227-2007-ESTUDOS-CLINICOS.pdf.

38. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 [Internet]. Official Journal of the European Union 2014 p. 1–76. [cited 2015 Jan 19]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

39. Clinical trials - General information [Internet]. European Commission. 2014 [cited 2015 Jan 13]. Available from: http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm#ct2.

40. PricewaterhouseCoopers. Ensaios Clínicos em Portugal [Internet]. 2013. p. 23–9. [cited 2015 Jan 16]. Available from: http://www.aibili.pt/ficheiros/EstudoInvestigClinica_em_Portugal_jun2013vf.pdf.

41. Estatísticas de Avaliação de Ensaios Clínicos pelo Infarmed - Evolução Anual 2005-2015 [Internet]. Infarmed. 2015 [cited 2015 Jan 16]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS/Evolu%E7%E3o Anual 2005 - 2015.

42. European Medicines Agency. Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency [Internet]. 2013. p. 20–3. [cited 2015 Jan 17]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf.

43. Investigação clínica em Portugal – desafios e constrangimentos: Intervenção do Secretário de Estado Adjunto do Ministro da Saúde em reunião sobre a Investigação Clínica, no CCB, dia 18 [Internet]. Portal da Saúde. 2013 [cited 2015 Jan 15]. Available from: http://www.portaldasaude.pt/portal/conteudos/a+saude+em+portugal/ministerio/comunicacao/discursos+e+intervencoes/investigacao+clinica+ccb.htm.

44. Patient Recruitment and Retention are Major Challenges for Clinical Trials in CNS [Internet]. Applied Clinical Trials. 2015 [cited 2015 Jan 29]. Available from: http://www.appliedclinicaltrialsonline.com/print/209555?page=full.

45. Long G, Works J. Innovation in the Biopharmaceutical Pipeline: A Multidimensional View [Internet]. 2013. p. 7–9. [cited 2015 Jan 19]. Available from: http://www.phrma.org/sites/default/files/pdf/2013innovationinthebiopharmaceuticalpipeline-analysisgroupfinal.pdf.

46. About This Study [Internet]. Enroll HD. 2014 [cited 2015 Jan 28]. Available from: https://www.enroll-hd.org/learn/about-this-study/.

47. Sense Park - Home [Internet]. Sense Park. 2014 [cited 2015 Jan 30]. Available from: http://www.sense-park.eu/index.php.

48. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 [Internet]. Official Journal of the European Union; 2010 p. 1–16. [cited 2015 Oct 1]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF.

49. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 [Internet]. Official Journal of the European Union; 2010 p. 74–99. [cited 2015 Oct 1]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf.

50. Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 [Internet]. Official Journal of the European Union; 2012 p. 5–25. [cited 2015 Oct 1]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF.

51. Decreto-Lei n.º 20/2013, de 14 de fevereiro [Internet]. 2013 p. 1–174. [cited 2015 Oct 1]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/LEGISLACAO/LEGISLACAO_FARMACEUTICA_COMPILADA/TITULO_III/TITULO_III_CAPITULO_I/035-G1_DL_20_2013_1ALT.pdf.

52. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 [Internet]. Official Journal of the European Union; 2012 p. 1–4. [cited 2015 Oct 1]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2012_26/dir_2012_26_en.pdf.

53. Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 [Internet]. Official Journal of the European Union; 2012 p. 38–40. [cited 2015 Oct 1]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2012_1027/reg_2012_1027_en.pdf.

54. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) [Internet]. 2014. p. 8–17. [cited 2015 Oct 1]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

55. Maria VA, Carmona R. Capítulo 2.1: Organização do Sistema Nacional de Farmacovigilância. Farmacovigilância em Portugal. 2003. p. 63–74.

56. Pal SN, Duncombe C, Falzon D, Olsson S. WHO Strategy for Collecting Safety Data in Public Health Programmes: Complementing Spontaneous Reporting Systems. Drug Saf [Internet]. 2013 Feb;36(2):75–81. [cited 2015 Apr 24]. Available from: http://link.springer.com/10.1007/s40264-012-0014-6.

57. International Conference for Harmonisation. MedDRA [Internet]. [cited 2015 Apr 25]. Available from: http://www.ich.org/products/meddra.html.

58. Caldeira D, Canastro M, Barra M, Ferreira A, Costa J, Pinto FJ, et al. Risk of Substantial Intraocular Bleeding With Novel Oral Anticoagulants: Systematic Review and Meta-analysis. JAMA Ophthalmol [Internet]. 2015;133(7):834–9. [cited 2015 Jul 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25950647.

59. About EHDN REGISTRY - Description [Internet]. European Huntington's Disease Network. [cited 2015 Apr 12]. Available from: http://www.euro-hd.net/html/registry/about/description.

60. European Commission. Recommendation on the content of the trial master file and archiving [Internet]. 2006. p. 2–11. [cited 2015 May 6]. Available from: http://ec.europa.eu/health/files/eudralex/vol-10/v10_chap5_en.pdf.

61. Interactive Response Technologies (IRTs) [Internet]. Clinical Trials Toolkit. 2015 [cited 2015 Jan 27]. Available from: http://www.ct-toolkit.ac.uk/glossary/interactive-response-technologies-irts.

62. University Hospitals Bristol - NHS Foundation Trust. Confidentiality agreements,

feasibility and site selection [Internet]. 2012 [cited 2015 Oct 1]. Available from: http://www.uhbristol.nhs.uk/research-innovation/commercial-research/information-for-researchers/confidentiality-agreements,-feasibility-and-site-selection/.

63. Hints & Tips No4 - Investigator Meetings. In: The Institute of Clinical Research [Internet]. [cited 2015 May 8]. Available from: http://www.icr-global.org/EasySiteWeb/GatewayLink.aspx?alId=2220.

64. North Bristol - NHS Trust. Site Initiation Visit (SIV) [Internet]. [cited 2015 Oct 1]. Available from: http://www.nbt.nhs.uk/research-and-innovation/running-your-study/site-initiation-visit-siv.

65. Latha M, Bellary S, Krishnankutty B. Basics of case report form designing in clinical research. Perspect Clin Res [Internet]. 2014;5(4):159. [cited 2015 May 12]. Available from: http://www.picronline.org/text.asp?2014/5/4/159/140555.

66. Rosenbaum D. Chapter 4: Interactions with the sponsor. Clinical Research Coordinator Handbook: Gcp Tools and Techniques (Practical clinical trials series). Interpharm Pr; 1996. p. 91–110.

67. Chow S-C, Liu J-P. Chapter 15: Clinical Data Management. Design and Analysis of Clinical Trials. 2nd Editio. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2003. p.639-41.

68. Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis (EXPAND) [Internet]. Clinical Trials - U.S. National Institutes of Health. 2013 [cited 2015 Feb 10]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01665144?term=A+multicenter%2C+randomized%2C+double-blind%2C+parallel-group%2C+placebo-controlled+variable+treatment+duration+study+evaluating+the+efficacy+and+safety+of+Siponimod+%28BAF312%29+in+patients+with+.

69. Friedman LM, Furberg CD, DeMets DL. Chapter 1: Introduction to Clinical Trials. Fundamentals of Clinical Trials. 4th ed. Springer; 2010. p. 1–18.

70. World Health Organization. Chapter 4: Pharmacovigilance in Drug Regulation. The Importance of Pharmacovigilance Safety Monitoring of medicinal products. 2002. p. 15–20.